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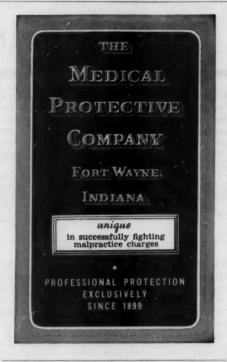
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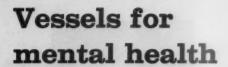


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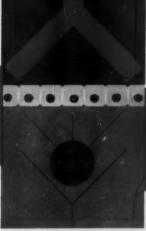
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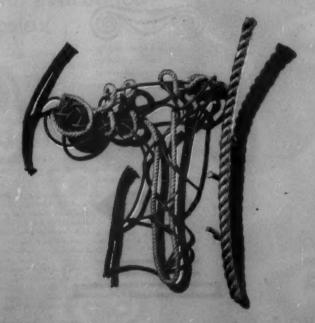
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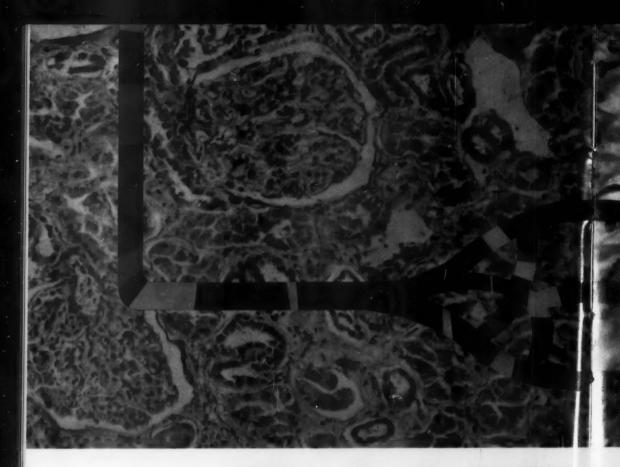
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Dosage: 2 to 6 tablets daily in divided doses initially; may be adjusted within range of 1 to 6 tablets daily in divided doses. Note: In hypertensive patients already on ganglionic blocking agents, veratrum and/or hydralazine, the addition of Rautrax necessitates an immediate dosage reduction of these agents by at least 50%. A similar reduction is also necessary when these ganglionic blocking agents are added to the Rautrax regimen.

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References: 1. Moyer, J.H., and others: Am. J. Cardiol., 3:113 (Jan.) 1959. • 2. Rodi, T., and others: To be published, Am. J. Cardiol., (April) 1959. • 3. Fuchs, M., and others: Monogruphs on Therapy, 4:43 (April) 1959. • 4. Montero, A.C.; Rochelle, J.B., III, and Ford, R.V.: To be published. • 5. Rochelle, J.B., III, Montero, A.C., and Ford, R.V.: To be published. • 6. Montero, A.C.; Rochelle, J.B., III, and Ford, R.V.: To be published. • 7. Doffermyer, L.R.; Byrd, C.W., and Lilly, W.H.: North Carolina M.J. 19:430 (Oct.) 1958.

Literature available on request.



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for your many patients requiring potent analgesia but not an injected narcotic

Proved by extensive evaluation<sup>1,2,3</sup> in 1998 patients in diverse areas of medicine and surgery, including: arthritis, bursitis, early metastatic carcinoma, fibrositis, grippe, herpes zoster, ligamental strain, low back pain, menstrual pain, myalgia, myositis, neuritis, pleurisy, postoperative pain, postpartum pain, sciatica, trauma, dental pain

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- prompt, potent action—as potent as codeine
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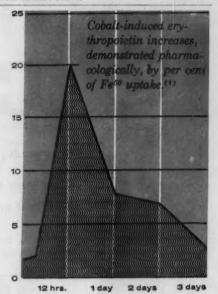
Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid. Philadelphia 1, Pa.



Cass, L.J., et al., J.A.M.A. 156:1829 (April 12) 1958.
 Batterman, R.G., et al., Am. J. M. Sc. 234:413 (Oct.) 1957.
 Medical Department, Wyeth: Final Report on the Clinical Evaluation of Zactirin.



Activates the physiologic mechanism in anemia therapy



# RONCOVITE-mf

Each tablet contains; Cobalt chloride (Cobalt as Co., 3.7 mg.)..15 mg., Ferrous Sulfate, exsiccated..100 mg.

Only cobalt among therapeutic agents enhances production of erythropoietin to promote red cell formation. 1,2,3

With Roncovite-MF, increased erythropoietin production permits excellent hematopoietic response with sharply reduced iron dosage.

Cobalt-iron (Roncovite therapy) has been demonstrated as superior to iron alone in the common hypochromic anemias such as menstrual anemia, anemia of pregnancy, nutritional anemia of infancy and refractory anemias of chronic infection. 4,5,6,7,8

(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Pizak, L. F.: Blood 13:55 (Jan.) 1958. (2) Gurney, C. W.; Jacobson, L. O. and Goldwasser, E.: Ann. Int. Med. 49:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C. and Bethell, F. H.: J. Lab. & Clin. Med. 52:364 (Sept.) 1958. (4) Ausman, D. C.: Journal - Lancet 76:290 (Oct.) 1958. (5) Holly, R. G.: Obst. & Gynec, 9:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec, 1:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinols M. J. Il3:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas State J. Med. 51:686 (Oct.) 1955.

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†Trademark for Tablets Protoveratrine A, 0.2 mg. and Reserpine, 0.08 mg. \*Patent Pending



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I was putting up my new cur-tains and draperies last week

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The step-stool wobbled . . . I fell and landed right on my

AND THE PAIN WENT AWAY FAST

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hours or more. MORE THOROUGH RELIEF — permits uninterrupted sleep through the night. RARELY CONSTI-PATES — excellent for chronic or bedridden patients. VERSATILE - new 'demi' strength permits dosage flexi-

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The response to an antidiarrheal preparation is directly linked to the effectiveness of its adsorbent. In both Polymagma and Polymagma Plain, the new agent Claysorb\* gives you a previously means more effective antidiarriteal treatment unattainable adsorptive power . . . proved **POLYMAGMA** For bacterial diarrheabactericidal against many pathogens **POLYMAGMA Plain** For nonbacterial diarrheasame formula but without antibiotics Polymagma Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb\* (Activated Attapulgite, Wyeth) in Alumina Gel



## in alcoholism1,2

ACUTE EMERGENCIES — a single intramuscular injection of 50 mg. (2 cc.) Vistaril Parenteral Solution is usually sufficient to calm the patient and initiate sound sleep. Vistaril is exceptionally well tolerated. Antiemetic action and absence of respiratory depression are among valuable assets reported.

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2. Paroxysmal Auricular Tachycardia



3. Paroxysmal Ventricular Tachycardia



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REFERENCES: 1. Miller, R. F.: Clinical Review, Vol. 1, No. 2 (July) 1958. 2. Van Gasse, J. J.: Clinical Medicine, 5:177-181 (Feb.) 1958. 3. Burrell, Z. L., et al.: Am. J. Cardiol., 1:624 (May) 1958. 4. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 116:451 (Dec.) 1956.

## in arrhythmias 3,4

Many types of cardiac arrhythmias respond promptly to oral, intramuscular or intravenous Vistaril therapy. Vistaril is particularly effective in ventricular extrasystoles, paroxysmal tachycardias (both auricular and ventricular), and ventricular extrasystoles complicating auricular fibrillation. The following dosage regimen is recommended:

PARENTERAL DOSAGE: 50-100 mg. (2-4 cc.) I.M. stat., and q. 4-6 h. p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

in acute emergency, 50-75 mg. (2-3 cc.) I.V. stat.; maintain with 25-50 mg. (1-2 cc.) I.V. q. 4-6 h. p.r.n.

ORAL DOSAGE: Initially, 100 mg. daily in divided doses until arrhythmia disappears. For maintenance or prophylaxis, 50-75 mg. daily in divided doses.

SUPPLY: Vistaril Capsules, 25 mg., 50 mg. and 100 mg. Vistaril Parenteral Solution, 10 cc. vials, and 2 cc. Steraject Cartridges, each cc. containing 25 mg. hydroxyzine hydrochloride.

2.2440

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# Do Not Confuse it with Tranquilizers

p-acetamidobenzoic acid salt of 2-dimethylaminoethanol

Deaner is a gentle, slow-acting antidepressant—a totally new molecule. It counteracts mild depression, thereby differing from tranquilizers or sedatives which may aggravate depression.

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Deaner also finds a broad area of usefulness in children with short attention span, behavior problems, and learning defects.

Contraindications: Grand mal epilepsy or mixed types of epilepsy with a grand mal component.

Dosage: Initially, 1 tablet (25 mg.) daily in the morning. Maintenance dose, 1 to 3 tablets; for children, 1/2 to 3 tablets. Full benefits may require two weeks or more of therapy.

'Deaner' is supplied in scored tablets containing 25 mg. of 2-dimethylaminoethanol as the p-acetamidobenzoic acid salt. In bottles of 100.

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and many other emotional and behavioral problems





Like oil on troubled waters

#### TABLETS - CAPSULES - ELIXIR - EXTENTABS

( <sup>7</sup>/<sub>4</sub> gr.) 16.2 mg ( <sup>3</sup>/<sub>4</sub> gr.) 48.6 mj

Prescribed by more physicians than any other antispasmodic

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"I seem to have the blues all the time ... I can't sleep ... "

in the depressed, unhappy patient

## PROMPTLY IMPROVES MOOD

without excitation

- · Acts fast to relieve depression and its common symptoms: sadness, crying, anorexia, listlessness, irritability, rumination, and insomnia.
- Restores normal sleep—without hang-over or depressive aftereffects. Usually eliminates need for sedative-hypnotics.

EFFICACY AND SAFETY CONFIRMED IN OVER 3,000 DOCUMENTED CASE HISTORIES.1,2,3

Dosage: Usual starting dose is I tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: Each light-pink, scored tablet contains 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HC1) and 400 mg. meprobamate.

- Alexander, L.: J.A.M.A. 166:1019, Merch 5, 1966.
  Current personal communications; in the files of Wallace La B. Pennington, V.M.; Am. J. Psychiat, 115:250, Sept. 1966.



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DOSAGE: Adults: CATHOMYCIN Sodium 2 capsules b.i.d. or CATHOMYCIN Calcium Syrup 4 teaspoonfuls b.i.d. Children: (up to 12 years) 2 to 8 teaspoonfuls daily in divided doses based on 10 mg. CATHOMYCIN per lb. of body weight per day.

SUPPLIED: Capsules sodium nevobiocin, each containing the equivalent of 250 mg. of novobiocin—vials of 16 and 100—and as an orange-flavored syrup (aqueous suspension), in bottles of 60 cc. and 473 cc. (1 pint). Each 5 cc. CATHOMYGIN Syrup contains 125 mg. (2.5%) novobiocin, as calcium novobiocin.

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now...for edema and hypertension See case history of this patient on following pages.



highest fluid yields, lowest blood-pressure levels yet achieved with oral diuretic-antihypertensive therapy...

ESIGPIX

(hydrochlorothiazide CIBA)



2/sessur-1



Record of patient with congestive failure, treated at a leading Philadelphia hospital. Photos used with permission of the patient.

marked pitting edema (4+) cleared in 4 days with Esidrix

#### ESIDRIX IS 10 TO 15 TIMES MORE ACTIVE THAN CHLOROTHIAZIDE

INDICATED IN...congestive heart
failure • hypertension • hypertensive
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DOSAGE: Esidrix is administered orally in an average dose of 75 to 100 mg. daily, with a range of 25 to 200 mg. A single dose may be given in the morning or tablets may be administered 2 or 3 times a day.

SUPPLIED: Tablets, 25 mg. (pink, scored); bottles of 100 and 1000. Tablets, 50 mg. (yellow, scored); bottles of 100 and 1000.





L.S., 81-year-old patient with complaint of painless hematuria admitted to hospital on 3/3/59. Past history included congestive heart failure of 15 years' duration. Clinically significant symptoms: expiratory wheezes over entire chest; bilateral coarse rales of both bases; slight abdominal distention (without evidence of ascites); palpable liver 2-3 fingerbreadths below rib cage; bilateral pitting edema (4+) of pretibial and ankle area. Admission diagnosis: hematuria of unknown origin; arteriosclerotic cardiovascular disease; poorly compensated heart failure; chronic pulmonary fibrosis with pulmonary insufficiency.



Patient was put on regimen of bed rest, moderate salt restriction, digitalis and pulmonary decongestants. When ankle edema, hepatic congestion and rales failed to clear by 3/6, Esidrix 50 mg. b.i.d. was ordered. By 3/8 L.S. had lost 3 pounds. Rales decreased; there was 1 + pitting edema of ankle area only. He felt more comfortable, was able to enjoy reading newspapers and magazines in bed.



By 3/11, patient's weight had dropped 2 more pounds. Ankle edema and lung rales were gone. Patient tolerated cystoscopy and fulguration of a small bleeding polyp in his bladder on 3/12 very well. Ambulatory on the 4th day of Esidrix therapy, L.S. visited his neighbors down the hall, played checkers with another patient. On 3/14 he was discharged.

Patient L.S. Date	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13
Urinary Output (ml.)	840	690	960	2140	1230	660	1220	1350		-
Weight (lbs.)	139	440,000	4	-	134	and the last		134	ecreto	-
Esidrix Dosage (mg./day)	0	0	50	100	100	100	100	100	50	100

## ESIGPIX (hydroch)

(hydrochlorothiazide CIBA)

- relieves edema in many patients refractory to other diuretics1
- often produces greater weight loss than parenteral mercurials or chlorothiazide<sup>2</sup>
- » provides a greater average reduction in blood pressure than chlorothiazide<sup>3</sup>
- is exceptionally safe...reduces the likelihood of electrolyte imbalance

1. Brest, A. N., and Likoff, W.: Am. J. Cardiol. 3:144 [Feb.] 1959. 2. Clark, G. M.: Clinical report to CIBA.
3. Dennis, E. W.: Clinical report to CIBA.

2/248489-2



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Each ENDURET prolonged-action tablet contains 75 mg, of active principle.
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DBI ( $N^1$ - $\beta$ -phenethylbiguanide HCl) is an entirely new oral hypoglycemic compound, different in chemical structure, mode of action, and in spectrum of activity from the sulfonylureas. DBI is usually effective in low dosage range (50 to 150 mg. per day).

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-DBI lowers elevated blood-sugar and eliminates glycosuria in *mild*, *moderate* and severe diabetes mellitus...

brittle diabetes, juvenile or adult — DBI combined with injected insulin improves regulation of the diabetes and helps prevent the wide excursions between hypoglycemic reactions and hyperglycemic ketoacidosis.

stable adult diabetes — satisfactory regulation of diabetes is often achieved with DBI alone without the necessity for insulin injections.

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primary and secondary sulfonylurea failures—DBI alone, or in conjunction with a sulfonylurea, often permits satisfactory regulation of diabetes in patients who have failed to respond initially or who have become resistant to oral sulfonylurea therapy.

smooth onset — less likelihood of severe hypoglycemic reaction—DBI has a smooth, gradual blood-sugar lowering effect, reaching a maximum in from 5 to 6 hours, and a return to pre-treatment levels usually in 10 to 12 hours.

safety—daily use of DBI in therapeutic dosage for varying periods up to 2½ years has produced no form of clinical toxicity.

side reactions—side reactions produced by DBI are chiefly gastrointestinal and occur with increasing frequency at higher dosage levels (exceeding 150 mg. per day). Anorexia, nausea or vomiting may occur—but these symptoms abate promptly upon reduction in dose or withdrawal of DBI.

supplied – DBI, 25 mg. scored, white tablets – bottle of 100.

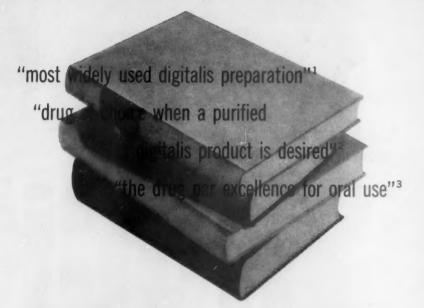
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(1) Gross, H., and Jezer, A.: Treatment of Heart Disease, Philadelphia, W. B. Saunders Company, 1956, p. 41. (2) Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2., New York, The Macmillan Company, 1956, p. 698.(3) Modell, W.: Drugs of Choice 1958-1959, St. Louis, C. V. Mosby Company, 1958, p. 441.

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# SHOCK

ARAMINE

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a superior vasopressor with a choice of routes for optimal response—no tissue slough observed

ARAMINE rapidly raises and maintains blood pressure in shock. Simplicity of administration with reported freedom from tissue slough, necrosis or thrombophlebitis<sup>1-4</sup> encourages its prompt use. Patients respond with increased glomerular filtration rate, renal blood flow and urinary output. Vasopressor effect is smooth and sustained with no secondary fall in blood pressure and no tachyphylactic response to repeated injections.

Versatile ARAMINE is indicated in shock accompanying anaphylaxis, myocardial infarction, brain damage and infectious disease, as well as hypotension due to hemorrhage, surgery and other factors that lead to shock.

supplied: in 1-cc. ampuls and 10-cc. vials (10 mg. per cc.).

references: 1. Am. J. M. Sc. 230:357, Oct. 1955.

2. Circulation 16:1096, Dec. 1957.

3. Circulation 13:834, June 1956.

4. J.A.M.A. 163:1482, April 20, 1957.

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MAALOX® an efficient antacid suspension of magnesium-aluminum hydroxide gel offered in bottles of 12 fluidounces.

TABLET MAALOX: 0.4 Gram (equivalent to one teaspoonful), Bottles of 100.

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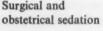
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## HIGHLIGHTS FROM THE A.M.A. COUNCIL ON DRUGS REPORT ON TRIAMCINOLONE

J.A.M.A. 169:257 (January 17) 1959.

"It [triamcinolone] has an anti-inflammatory potency greater than an equal amount of prednisolone; i.e., comparable suppressive effects may usually be achieved with lower doses of triamcinolone than with prednisolone."

"Triamcinolone lacks the sodium-retaining and edema-producing effects of most other glucocorticoids. During the first several days of administration, it may cause a loss of sodium from the body; an initial mild diuretic action is frequently observed, whether the patient is frankly edematous or not. This is in contrast to the definite sodium-retaining and fluid-retaining properties of cortisone and hydrocortisone and to a much lesser extent with prednisone and prednisolone."

"Except in exceedingly large doses, triamcinolone apparently has no consistent effect on potassium excretion. Hence, neither sodium restriction nor potassium supplementation is ordinarily required during therapy with this agent."

"As with other glucocorticoids, the long-term administration of triamcinolone results in definite catabolic effects, as indicated by impairment of carbohydrate utilization and negative protein and calcium balance. This catabolic effect, coupled with a lack of appetite stimulation which is apparently peculiar to triamcinolone, may produce weight loss that might be undesirable in some patients treated for long periods of time."

"...the voracious appetite, with weight gain and euphoria, characteristic of other steroids, is not seen with administration of triamcinolone."

"Triamcinolone has been used for the management of a wide variety of clinical conditions usually considered amenable to systemic steroid therapy. These have included rheumatoid arthritis and other collagen diseases, allergic and dermatological disorders, certain leukemias and malignant lymphomas, the nephrotic syndrome, pulmonary emphysema and fibrosis, acute bursitis, rheumatic fever, and certain blood dyscrasias. Although clinical experience with the drug in some of the foregoing conditions is not extensive, the many similarities in action between triamcinolone and other potent glucocorticoids would indicate a usefulness for triamcinolone akin to that of other agents of this class."

"There is some evidence that triamcinolone is more effective at a smaller dosage than are other steroids in controlling both the skin and joint lesions in psoriasis, whether or not complicated by arthropathy."

"Triamcinolone appears to compare favorably with other steroids for use in those situations in which edema and sodium retention have been complicating problems."

"It [triamcinolone] may also be the steroid of choice for patients in whom psychic stimulation, euphoria, voracious appetite, and weight gain should be avoided."

"...the drug [triamcinolone] does produce the other side effects and untoward reactions common to the glucocorticoids. At therapeutically equivalent doses, the frequency and severity of clinical manifestations of hyperadrenalism — rounding of the face, fat deposition, and hirsutism — are essentially the same. Likewise, there is little indication that the relative incidence of osteoporosis is materially decreased after the long-term use of the drug."

"Triamcinolone apparently does not cause the euphoria sometimes seen with other steroids, and the occurrence of mental depressions is uncommon."

"Current evidence suggests that the drug [triamcinolone] may not produce as high an incidence of peptic ulcer as do other steroids."

"Cutaneous erythema seems to be a side effect peculiar to triamcinolone."

"The usual contraindications and precautions of glucocorticoid therapy should be followed in the use of triamcinolone, keeping in mind that prolonged therapy with this drug will suppress the function of the patient's own adrenals by interfering with the pituitary-adrenal axis."



Supplied: 1 mg. scored tablets (yellow) 2 mg. scored tablets (pink)

4 mg. scored tablets (white)



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

#### STOP

#### SPASM

#### PAIN

#### DEPRESSION

In LOW-BACK ACHE

DISIDAL

Brand of Orphenadrine HCI

#### In Parkinsonism

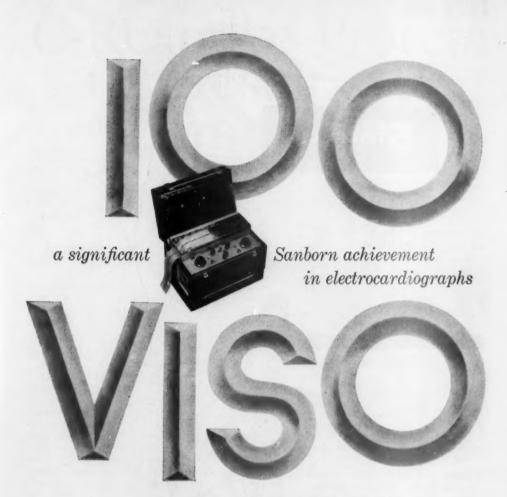
Highly selective action...energizing against weakness, fatigue, adynamia and akinesia...potent against sialorrhea, diaphoresis, oculogyria and blepharospasm... lessens rigidity and tremor... alleviates depression...safe ...even in glaucoma.

\*Trademark of Brocedes-Stheeman & Phermacis. U.S. Patent No. 2,567,351. Other patents pending In muscle spasm due to sprains, strains, herniated intervertebral disc, fibrositis, noninflammatory arthritic states and many other musculoskeletal disorders, the first demand is for relief. Disipal fills this need. It is quickly effective in skeletal muscle spasm almost regardless of origin. Its mood-alleviating effect braces the patient against the depression so often accompanying severe pain of any type.

Dosage: 1 tablet (50 mg.) t.i.d.



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Here is an electrocardiograph in which no detail has been overlooked to give you diagnostically accurate information...the greatest possible operating convenience... and modern, functional attractiveness. With thirty-five years of experience, this is the finest electrocardiograph Sanborn Company has ever produced. Priced at eight hundred fifty dollars, delivered continental U.S. A.

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Chemically unlike any other muscle relaxant, Sinaxar is

- consistently effective in the majority of cases
- · long acting: no fleeting effects
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DOSAGE: Two tablets three or four times daily.

SUPPLIED: 200 mg. tablets in bottles of 50.

INDICATIONS: Any condition involving skeletal muscle spasm, as musculoskeletal disorders: acute and chronic back ache; arthritides; bursitis; disc syndrome; fibrositis; myalgia; myositis; osteoarthritis; following orthopedic procedures; rheumatoid arthritis; spondylitis; sprains and strains; torticollis; neurologic disorders: cerebral palsy; cerebrovascular accidents; cervical root syndrome: multiple sclerosis.

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#### SCREENING TEST

Mix one drop of serum specimen with two drops of CR-TEST reagent on glass slide. Presence of C-reactive protein will be indicated within one to two minutes by easily visible flocculation.

#### **OUANTITATIVE TEST**

Levels of C-reactive protein are equally easy to determine. Prepare serum dilutions of test specimen in buffered diluent. On successive sections of glass slide, mix one drop of CR-TEST reagent with one drop of each serum dilution. The highest dilution showing visible flocculation within two minutes is taken as the C-reactive protein titer of the specimen.

#### SUPPLIED

Kits containing Latex-Anti-C-Reactive Protein Reagent, Glycine-Saline Buffer Diluent for serum dilution, capillary pipettes for serum transfer, and 2 divided glass slides. Each kit sufficient for 60 screening tests. \$10.00 per kit. Also available: CR-TEST Positive Control Serum, 0.5 cc.



## Hyland CR-TEST\*



HYLAND LABORATORIES 4501 Colorado Blvd., Los Angeles 39, Calif. 160 Lockwood Ave., Yonkers, N.Y.

\*Trade Mark of Hyland Laboratories

## announcing

## PROZINE

meprobamate and promazine hydrochloride, Wyeth

### SPECIFIC CONTROL OF EMOTIONAL DISTURBANCES

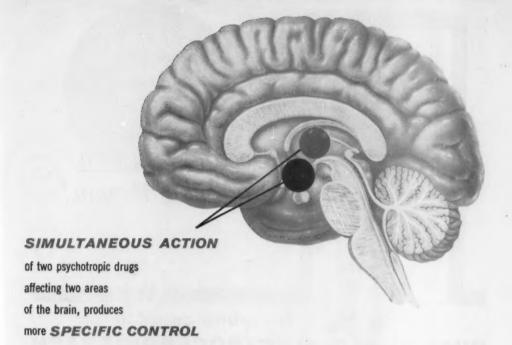
#### THROUGH DUAL ACTION

PROZINE controls anxiety and tension as well as motor excitability. This effect on the components of emotional reaction is possible because of the dual sites of action of PROZINE—the thalamic and hypothalamic areas of the brain. The unique dual action of PROZINE enables the physician to exert more specific control over emotionally disturbed patients.

PROZINE controls emotional disturbances manifested by apprehension and agitation, insomnia, nausea and vomiting, gastrointestinal symptoms, alcoholism, menopausal symptoms, premenstrual tension.

PROZINE is indicated in patients having a primary emotional disturbance, in patients having an emotional disturbance unrelated to their organic disease, and in patients emotionally disturbed by primary organic disease. PROZINE is especially useful in overly apprehensive medical patients—including surgical and obstetrical—and in emotional problems of children, adolescents, and the aged. It also is useful in emotionally disturbed patients who receive little or no relief from analgesics, barbiturates, anticholinergics, antihypertensives, and hormones (estrogens and corticoids).

A STATE OF THE PARTY OF THE PAR



**PROZINE** in the recommended dosage (1 or 2 capsules, 3 or 4 times daily) produces more specific control than is obtainable with high doses of other ataractic agents.

thus

In emotionally disturbed patients on PROZINE the dose required is diminished to the point where the incidence of side-effects and toxicity reactions is minimal\* and the patient is calm, tranquil, and amenable to additional therapy, whether it be educational, medical, or psychiatric.

Supplied: Bottles of 50 capsules, each containing 200 mg. of meprobamate and 25 mg. of promazine hydrochloride. Comprehensive literature available



\*In studies involving 972 patients suffering a variety of emotional diseases, related and unrelated to physical ailments, 78 per cent were improved; the incidence of side-effects was only 3.7 per cent.



Doctor, you can take it with you!

THE BURDICK EK-III

#### DUAL-SPEED ELECTROCARDIOGRAPH

• 261/2 pounds light, including all accessories and carrying case! Ideal for office or bedside use

• 25 or 50 mm. speed an accurate record for an accurate diagnosis

• frequency response greatly in excess of minimum A.M.A. standards

 top-loading paper drive eliminates tedious paper-threading adjustments



For complete informa-tion on the Dual-Speed EK-III, please write for "New Horizons in Electrocardiography"no obligation.



THE BURDICK CORPORATION
MILTON, WISCONSIN
Brunch Offices: New York \* Chicogo \* Atlanta \* Los Angeles



protects against anginal attacks

RUSSEK: PETN is "....
the most effective drug currently available for prolonged prophylactic treatment of angina pe-toris." Prevents some 80% of anginal attacks.



eases cardiac tension

RUSSEK: "I favor ATARAX [as the tranquilizer for the aprious cardiac] ... because there is an absence of side-effects with this drug, and also because in cardiacs who are troubled with actoric beats, ATARAX has a quinidire like artice."



CARTRA

Dosage: Begin with 1 to 2 yellow CARTRAX "10" tab-lets (10 mg. Petn plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. Petn plus 10 mg. ATARAX).

For convenience, write "CARTRAX 10" or "CARTRAX 20."

Supplied: In bottles of 100.

References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Minmi Beach, April 12, 1966.



New York 17, N.Y. Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being

Can antacid therapy be made more effective?



ANNOUNCING

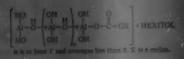
THE MOST SIGNIFICANT IMPROVEMENT IN ANTACID THERAPY SINCE THE INTRODUCTION OF ALUMINUM HYDROXIDE IN 1929

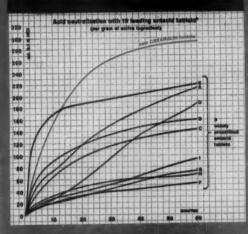
Creamalin

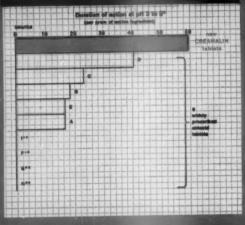
Each Creamalin Antacid Tablet contains 320 mg. specially processed, highly reactive, short polymer dried aluminum hydroxide gel, stabilized with hexital, with 75 mg. magnesium hydroxide.

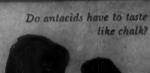
- 1. Neutralizes acid faster (quicker relief)
- 2. Neutralizes more acid (greater relief)
- 3. Neutralizes acid longer (more lasting relief)
- 4. No constipation · No acid rebound
- 5. More pleasant to take

#### a new high in effectiveness and palatability













No chalky taste. New CREAMALIN tablets are not chalky, gritty, rough or dry. They are highly palatable, soft, smooth, easy to chew, mint flavored.

NO ACID REBOUND . NO CONSTIPATION . NO SYSTEMIC EFFECT

Adult Dosege: Gestric hyperacidity: 2 to 4 tablets as necessary. Peptic ulcer or gastritis: 2 to 4 tablets every two to four hours. Tablets may be cheesed. swallowed with water or milk, or allowed to dis-solve in the mouth.

Supplied: Bottles of 50, 100, 200 and 1000.

### new for total management of itching; inflamed; infected<sup>56</sup> skin lesions



Cleared in 5 days

## Nycolog Kenalog, Spectrocin and Mycostatin in Plastibase Ointment

antipruritic/anti-inflammatory/antibacterial/antifungal

Mycolog Ointment – containing the new superior topical corticoid Kenalog – reduces inflammation, 3.4 relieves itching, 1.2 and combats or prevents bacterial, monilial and mixed infections. 5.7 It is extremely well tolerated, and assures a rapid, decisive clinical response for most infected dermatoses.

"Thirty-one of 38 patients... obtained excellent or good control of dermatological lesions... [Mycolog] was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2-to 3 weeks."\*

For total management of itching, inflamed, infected skin lesions, Mycolog contains triamcinolone acetonide, an outstanding new topical corticoid for prompt, effective relief of itching, burning and inflammation<sup>1-4</sup> — neomycin and gramicidin for powerful antibacterial action<sup>7</sup> — and nystatin for treating or preventing Candida (Monilia) albicans infections.<sup>6-9</sup>

Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1%) triam-cinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in examase.

References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. - 2. Nis, T.E., Jr., and Derbes, V.J.:
Monographs on Therapy 3:123 (Nov.) 1958. - 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July)
1958. - 4. Sternberg, T.H.: Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1956. - 5.
Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:13 (Nov.) 1958. - 8.
Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. - 9. Bereston, E.S.: South, M.J. 50:47 (April) 1957.
And whatever the topical corticoid need, a suitable Squibb formulation is available—Renalogs: Eutomo—7½ cc.
plastic squeeze bottles. Each cc. supplies 1.0 mg. (0.1%) Iriamcinolone acetonide, 2.5 mg. neomycin base and
0.25 mg. gramicidin. Kenalog Cream, 0.7%—5 Gm. and 15 Gm. tubes. Kenalog Lotton, 0.1%—15 cc. plastic squeeze bottles. Kenalog Ointment, 0.1%—5 Gm. and 15 Gm. tubes.



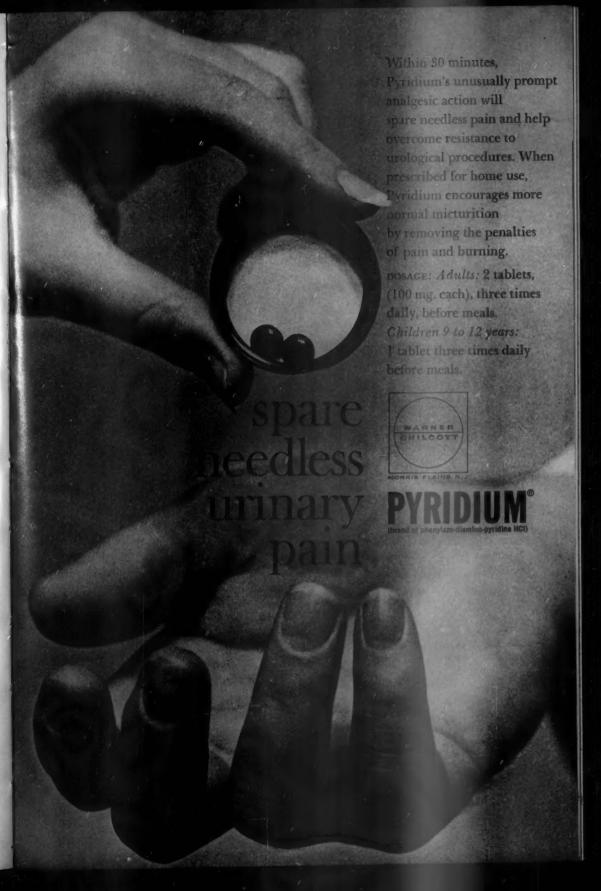
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Squibb Quality - the Priceless Ingredient

"REPERTNOCHE", "MYCOSTATIN"S, "PLASTISASE"S, "MYCOLOG" AND "MCMACOS" AND STADEMARD



#### THE HEART DISEASE PATIENT NEEDS RELIEF FROM

**EMOTIONAL** STRESS



ANXIETY INTENSIFIES the physical disorder in heart disease. "The prognosis depends largely on the ability of the physician to control the anxiety factor, as well as the somatic disease." (Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.)

Available in 400 mg. scored and 200 mg. sugarcoated tablets. Also available as MEPROSPAN\* (200 mg. meprobamate continuous release capsules). In combination with a nitrate, for angina pectoris: MILTRATE\*-(Miltown 200 mg. + PETN 10 mg.).

TRANQUILIZATION WITH MILTOWN enhances recovery from acute cardiac episodes and makes patients more amenable to necessary limitations of activities.

(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

Miltown causes no adverse effects on heart rate, blood pressure, respiration or other autonomic functions.

WALLACE LABORATORIES, New Brunswick, N. J.

arrest acute urinary infection Pyridium Tri-Sulfa combine the efficacy of the classic triple sulfas with the full analgesic dosage of Pyridium. Relief of pain is prompt—within 30 minutes—and therapeutic sulfonamide levels are obtained within hours.

#### FORMULA:

Pyridium, 150.0 mg. (2½ gr.); (brand of phenylazo-diamino-pyridine HCl) Sulfadiazine, 167.0 mg. (2½ gr.); Sulfamerazine, 167.0 mg. (2½ gr.); Sulfamethazine, 167.0 mg. (2½ gr.).

DOSAGE: Adults: 1 tablet four times daily.



PYRIDIUM° TRI-SULFA

### B. I. D.

ULCER CONTROL

all day

DARIC ON TABLETS

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#### patient comfort

Natural Prolonged Action—The action of DARICON, a more potent and better tolerated anticholinergic, is consistently prolonged because it has a unique chemical structure and is not dependent on "mechanical" means (e.g., special coating, adsorption on ion-exchange resin).

In addition to peptic ulcer, DARICON, is also indicated for other gastrointestinal disorders characterized by hypersecretion, hypermotility and spasm (e.g., functional bowel syndrome. chronic nonspecific ulcerative colitis and biliary tract disease).

Dosage: 10 mg. b.i.d. (morning and evening). Supply: Tablets, 10 mg., white, scored. Bottles of 60 and 500.

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Plizer Science for the world's well-being



EVEN REFRACTORY CASES RESPOND

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

Mandelamine's therapeutic distinction stems from its ability to control chronic urinary infections, including those resistant to antibiotics.

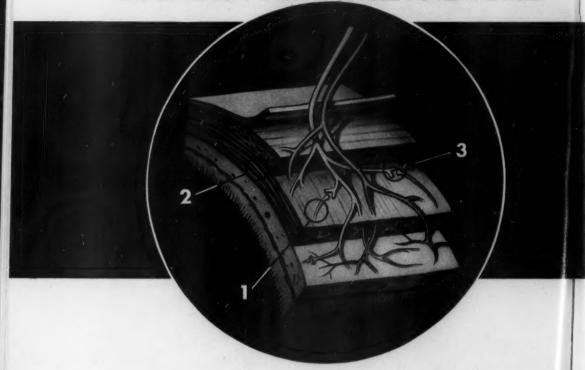
Mandelamine suits all age groups but it is particularly useful in older patients. Its antibacterial action is confined to the urinary tract; sensitization is unlikely; no fluids or alkalies are needed and cost is most economical.

DOSAGE: Adults: Average initial dosage is 1.0 to 1.5 Gm. four times daily. Children over five: 0.5 Gm. four times daily.



MANDELAMINE

## UNIQUE THREE-WAY CONTROL OF SMOOTH MUSCLE SPASM WITH A SINGLE POTENT DRUG



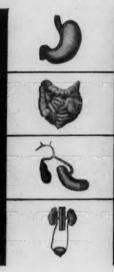
- 1 ANTICHOLINERGIC inhibition of parasympathetic stimuli
- 2 MUSCULOTROPIC spasmolytic action directly on smooth muscle
- 3 GANGLION-BLOCKING action at synaptic level

## MUREL

IN SMOOTH MUSCLE SPASM

Please Mention this Journal when writing to Advertisers

"potent in relaxing the spasm of smooth muscle whether in the G. J., or G. U. tracts, or the gallbladder." 1



in peptic ulcer - breaks the chain reaction of spasm-pain

in (i.l. spain – severe convulsive pain and vomiting re ported eliminated or substantially improved without unpleasant side effects or toxic reactions

in biliary spasia and chronic cholecystopathies with o without stones - excellent response promptly achieved

in (r, U) spasm—in postoperative spasm, cystitis, and pyelitis effective relief of pain and spasm was noted in all of a series of 75 patients

Effective and well tolerated..."MUREL" provides decisive relief without drug-induced complications; its coordinated three-way action permits significantly low dosage and minimizes reaction potential of any one mechanism; rapidly detoxified and excreted, avoiding cumulative effects. With average therapeutic dosages, there were no side effects such as mouth dryness, visual disturbances, interference with micturition, or bowel evacuation.<sup>2</sup>

Dosage: Mild to moderate cases: initially, 1 or 2 tablets four times daily. Acute or severe cases: 1 to 2 cc. (10-20 mg.) intravenously or intramuscularly every four to six hours up to maximum of 60 mg. in 24 hour period. The higher dosage range is usually required in spasm of the G.U. and biliary tract.

Supplied: "MUREL" Tablets — 10 mg. Valethamate bromide, bottles of 100 and 1,000. "MUREL" Injectable — 10 mg. per cc., vials of 5 cc. (Also available: "MUREL" with Phenobarbital Tablets — 10 mg. Valethamate bromide with ¼ gr. phenobarbital per tablet, bottles of 100 and 1,000.)

Holbrook, A. A.: Report abstracted in M. Science 4:46 (July 10) 1958.
 Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955.
 Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955.
 Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.



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- Prompt remission of symptoms
- Bleeding and frequency of stools sharply reduced
- Healing of rectal mucosa within a month in most cases
- Can be given safely over long periods of time

At zulfidine R BRAND OF SALICYLAZOSULFAPYRIDINE

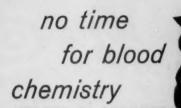
the most
valuable drug
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Ulcerative Colitis "The most widely accepted sulfonamide preparation today for the therapy of chronic ulcerative colitis is salicylazosulfapyridine [Azulfidine)."

Hightower, N.C., Jr., and others; Am. J. Digest. Dis.: 3:931 (Dec.) 1958

Also valuable in treatment of regional enteritis and other forms of colitis

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Often there is no time to wait for blood chemistry studies in the emergency treatment of shock, burns or trauma. The need is for immediate restoration of circulating plasma volume.

ALBUMISOL fills this need ideally—with albumin, the protein responsible for most of the osmotic pressure of plasma. The use of ALBUMISOL involves no risk of serum hepatitis. ALBUMISOL may be administered as rapidly as the clinical situation warrants.

ALBUMISOL is also valuable in hypoproteinemia to relieve edema and maintain plasma volume at normal levels. ALBUMISOL 25% (salt-poor) provides a combined attack on the nutritive deficiencies and severe fluid retention of advanced cirrhosis and nephrosis.

Supplied: ALBUMISOL 5% in 250 cc. and 500 cc. bottles. ALBUMISOL 25% (salt-poor) in 20 cc. and 50 cc. bottles.

## Albumisol

ready for immediate blood volume replacement

ALBUMISOL is a trademark of Merck & Co., INC.



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in skeletal-muscle disabilities . . .

#### for whole-patient response in spasm,

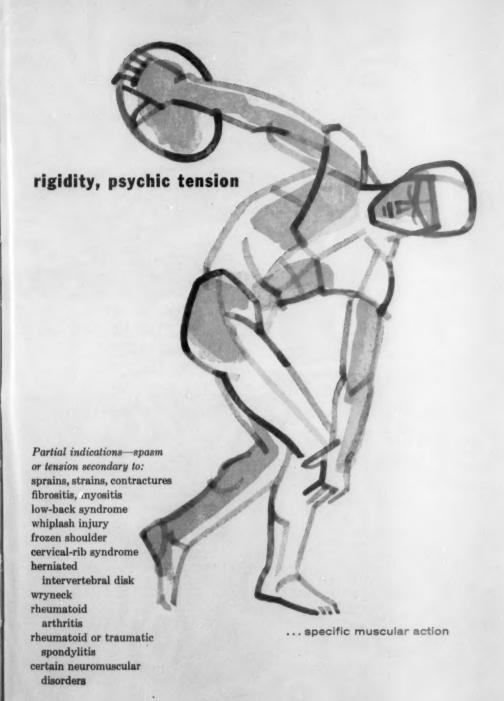
Of all muscle relaxants in current use, only meprobamate is supported by hundreds of clinical studies that demonstrate relaxing action on both brain and skeletal musculature. This is why EQUANIL stands as the obvious choice of many physicians concerned with whole-patient response. EQUANIL reduces muscular spasm and tension, aids in the restoration of mobility, speeds rehabilitation, lessens the emotional overlay.<sup>1-6</sup> Its margin of safety is shared by few agents in medical practice.

1. Mitchell, E.H.: M. Ann. District of Columbia 27:190 (April) 1958. 2. Cooper, C.D., and Epstein, J.H.: Am. J. M. Sc. 235:448 (April) 1958. 3. Vazuka, F.A.: Neurology 8:446 (June) 1958. 4. Cobey, M.C.: Am. Surgeon 24:350 (April) 1958. 5, 6. Wein, A.B.: M. Ann. District of Columbia 27:346 (July) 1958; Clin. Med. 6:44 (Jan.) 1959.





... specific central action



#### even if your patient is a boom rat



Showers who raths have in a Chamera's

he'll be pulling down his pay again soon thanks to

(PARALLENS + TYLENOLS)

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McNeil Laboratories, Inc & Philadelphia (2) Par

prescribe Pararos in low back pain

Each PARAYON tablet containts
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Each Evicities and the first area state and 12, mg. Tylexola accommodate 500 mg, and predissolone 1.0 mg.

Supplied: Tablets, scored, buff colored bottles of 36.

Precautions: The precautions and contra indications that apply to all steroids should be kept in mind when prescribing PARAFOT

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your patients can have POLARAMINE ... the newest antihistamine

.in a pleasant-

it's aprimint

tasting syrup

FOR THE YOUNG, THE ELDERLY and THOSE WHO PREFER LIQUID MEDICATION

> Your most discriminating patients will be pleased with the new, delicious-tasting Polaramine Syrup. POLARAMINE provides greater therapeutic effectiveness at lower dosages than other antihistamines -- and has a lower incidence of the usual antihistamine side effects.

> > POLARAMINE Syrup is compatible with many frequently prescribed medications.

#### DOSAGE

Adult, one teaspoonful t.i.d. or q.i.d. Children under 12, one-half teaspoonful t.i.d. or q.i.d. Infants, one-quarter teaspoonful t.i.d. or q.i.d.

#### HOW SUPPLIED

2 mg./5 cc., bottles of 16 oz.

## DLARA

SYRUP

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†Apricot-mint flavored

Schering

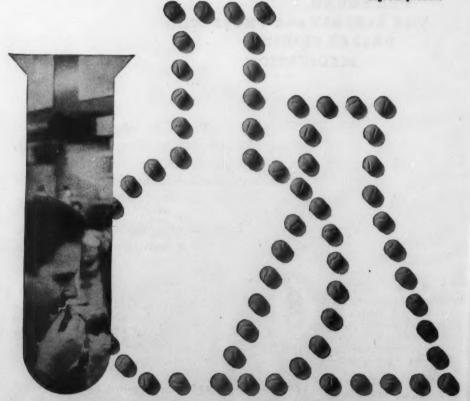
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Armour thyroid tablets assure: Consistent response—unsurpassed quality—highest manufacturing standards—full potency up to 17 years of storage—dependable therapy in: frank thyroid deficiencies and when hypothyroidism is associated with chronic recurrent colds, functional menstrual disorders, sterility, habitual abortion, obesity, hypometabolism. Thyroid is recommended in long-term therapy with ACTH or corticosteroids. Supplied in \( \frac{1}{4}, \frac{1}{2}, 1, 2 \) and 5 grain strengths.

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the most
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PHYSICAL TRAUMA - INJECTION HYDEL-TRASOL meets the demands of sudden stress by



BLOOD TRANSFUSION—in addition to



In your bag.. ready for use ... IMMEDIATELY!

THE FIRST READY-TO-USE. SOLUBLE. **ALL-PURPOSE** PARENTERAL STEROID

INJECTION HYDELTRAS

#### ADVANTAGES:

- 1. Immediately effective-dramatic response in minutes
- 2. Ready for use-needs no reconstitution or refrigeration
- 3. In solution—flows readily through a small-bore needle

SUPPLIED: In 2-cc. and 5-cc. vials, each cc. containing 20 mg. of prednisolone 21-phosphate as the di-sodium solt. Hydelfresol is a tradomerk of Merck & Co., Inc.

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In 8 out of 10 patients
Complete Control of
Grand Mal Soizures

# "MYSOLINE"

wide margin of safety

### Composite Results of 20 Clinical Studies

/ Results in 262 epiteptic patients when "Mycoline" was used alone.					
Type of Seizure	Number of Patients	Completely Controlled	50-90% Improved	<50%	
Grand Mal Psychomotor Focal Jacksonian	214 29 19	172 (80%) 19 (65%) 19 (100%)	15 (7%)	27 (13%) 10 (35%)	

Results in 653 epileptic parients who had failed to respond successfully to other anticonvulsants. "Mysoline" was added to current medication which, in some cases, was eventually replaced by

Type of Seizure	Number of Patients	Completely Controlled	50-90% Improved	<50%
Grand Mal Psychomotor	613 130	175 (28.5%) 10 (7.7%)	253 (41.2%) 65 (50%)	185 (30.3%) 55 (42.3%)
Focal Jacksonian	92	14 (15.2%)		42 (45.7%)

The dramatic results obtained with "Mysoline" advocate its use as first choice of effective and safe therapy in the control of grand mal and psychomotor attacks.

SUPPLIED: 0.25 Gm. scored tablets, bottles of 100 and 1,000.

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Complete food, Mead Johnson powder

When you prescribe Sustagen during convalescence, you help fulfill the critical needs of your patients for increased amounts of calories, protein and vitamins. "In some instances of acute illnesses, injury, or surgery, intensive nutritional therapy may be the deciding factor in the outcome." Sustagen, because it generously supplies all known essential nutrients in convenient concentrated form, helps speed recovery.



\*Halpern, S. L.: Ann. New York Acad. Sc. 63: 147-164 (Oct. 98) 1986.

- postoperatively
- · in pregnancy when vomiting is persistent
- following neurosurgical diagnostic procedures
- in infections, intra-abdominal disease, and carcinomatosis
- after nitrogen mustard therapy

# for nausea and vomiting

- · provides prompt, potent, and long-lasting control
- · capable of depressing the gag reflex
- · effective in cases refractory to other potent antiemetic agents
- · may be given intravenously, intramuscularly and orally
- · no pain or irritation on injection

ANTIEMETIC DOSAGE: Intravenous: 8 mg. average single dose Dosage range 2-10 mg.
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Parenteral solution — 1 cc. ampuls (20 mg./cc.), 1 cc. multiple dose vials (20 mg./cc.)

Oral tablets — 10 mg., 25 mg., 50 mg., in bottles of 50 and 500





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tablets · alka capsules

potent · nonhormonal · anti-inflammatory agent

BUTAZOLIDIN tablets or the Alka capsules are equally effective but individually adaptable in a wide range of arthritic disorders.

Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

Gouty Arthritis: "...95 per cent of patients experienced a satisfactory re-Sponse ..."1

Rheumatoid Arthritis: In "A total of showed at least major improvement, per cent minor improvement...."3

with 21.8 per cent showing minor improvement..." Osteoarthritis: 301 cases showed "...a total of 44.5 per cent with complete remission or major improvement. Of the remainder, 28.2 per cent showed minor improvement...." Spondylitis: All patients ... experienced initial major improvement that was maintained throughout the period of medication."5 Painful Shoulder Syndrome: Response of 70 patients with various forms showed "...8.6 per cent complete remissions, 215 cases...over half, 50.7 per cent 47.1 per cent major improvement, 20.0

References: 1. Graham, W.: Canad. M. A. J. 79:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. 8:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. 256:388, 1957.

Availability BUTAZOLIDIN® (phenylbutazone ggiev): Red coated tablets of 100 mg. BUTAZOLIDINO Alka: Capsules containing BUTAZOLIDINO (phenylbutazone egiqv), 100 mg.: dried aluminum hydroxide gel. 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide, 1.25 mg

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in all diarrheas

MOMYCIN

EXPERIENCE

MORE THAN 16 MILLION DOSES ERED WITH

regardless of etiology



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# reduces inal attacks

protects against pain by sustained coronary vasodilatation and control of complicating and triggering emotions

reduces fear of attacks
reduces severity of attacks
reduces frequency of attacks
reduces dependence on nitroglycerin
increases workload tolerance

Supplied: Tablets, vials of 50. Each tablet contains 200 mg. of meprobamate and 10 mg. of pentaerythritol tetranitrate.

Meprobamate and Pentaerythritol Tetranitrate, Wyeth

Wyeth

Philadelphia I. F

Inc.

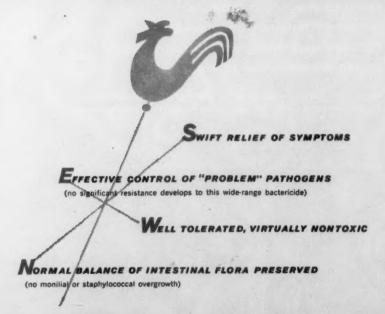
## TO STOP DIARRHEA

from all points...growing evidence favors

## FUROXONE

brand of furazolidone

■ Pleasant-flavored Liquid, 50 mg. per 15 cc. (with kaolin and pectin) ■ Convenient Tablets, 100 mg. ■ Dosage—400 mg. daily for adults, 5 mg./Kg. daily for children (in 4 divided doses).



From a Large Midwestern University: FUROXONE Controls Antiblotic-Resistant Outbreak. An outbreak of bacillary dysentery due to Shigella sonnei was successfully controlled with FUROXONE after a broad-spectrum antibiotic had proved inadequate. Cure rates (verified by stool culture) were 87% with FUROXONE, 36% with chloramphenicol. Only FUROXONE "failures" were those lost to follow-up. Chloramphenicol failures subsequently treated with FUROXONE responded without exception. FUROXONE was also used effectively as prophylaxis and to eliminate the carrier state. It was "extremely well tolerated in all 191 individuals who received it either prophylactically or therapeutically."

Galcota, W. R., and Moranville., B. A.: Student Medicine (in press)

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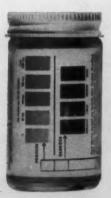
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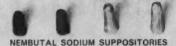
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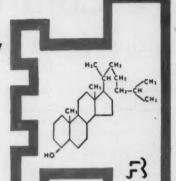
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1. Morrison, L. M., Serum Cholesterol Reduction with Lecithin; Geriatrics, 13:12 (Jan.) 1958. 2. Wittcoff, H., The Phosphatides; A.C.S. Monograph Series #112; Reinhold Pub. Corp. NYC 1951. 3. Bloor, W. R., Biochemistry of the Fatty Acids; A.C.S. Monograph Series #93, Reinhold Pub. Corp. NYC 1943. 4. Article, Lecithin in the Diet; Journal A.M.A. 168:1168 (Oct. 25) 1958.



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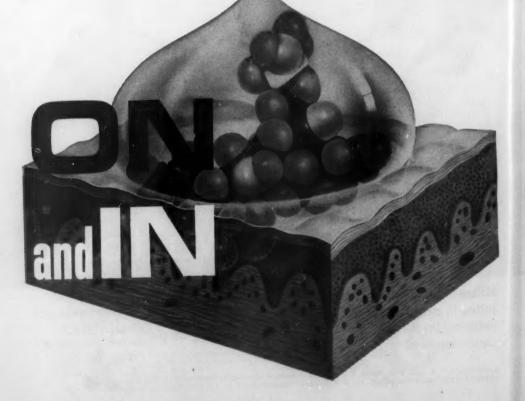
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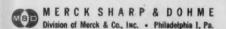
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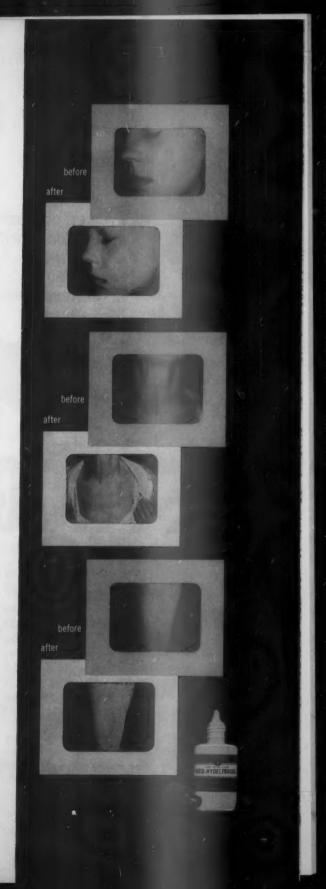
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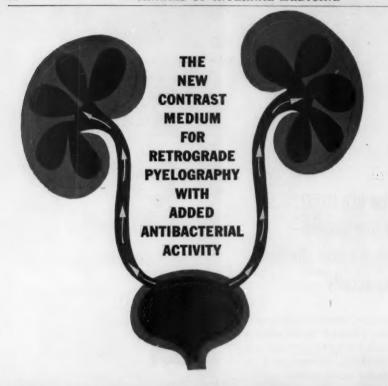
1. Shelmire, J. B., Jr.: A.M.A. Arch. Dermat. 78:191, August 1958.

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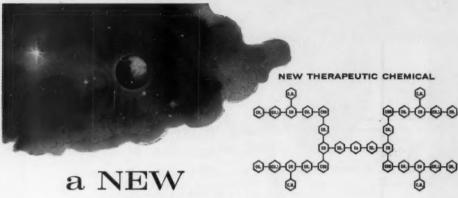
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References: 1. McHardy, G., et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, California, January 27, 1958. 2. Strub, I. H., and Carballo, A.: To be published. 3. Schuller, E.: Gaz. des Höpitaux 10:391 (Apr. 10) 1957. 4. Farah, L.: Internat. Rec. Med. 169:379 (June) 1956. 3. La Barre, J.: Compt. rend. Soc. Biol. (Paris) 150:1807 (Oct.) 1956. 6. Harrisson, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957. 7. Data in Roerig Medical Department files.



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2. Soss, T. L.: California Med. 87:266, 1957.

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## ANNALS OF INTERNAL MEDICINE

VOLUME 50

MAY, 1959

Number 5

#### ZINC METABOLISM IN HEPATIC DYSFUNCTION \* †

By BERT L. VALLEE, M.D., WARREN E. C. WACKER, M.D., ANTHONY F. BARTHOLOMAY, Sc.D., and FREDERIC L. HOCH, M.D., Boston, Massachusetts

ZINC is present in all living organisms and is essential as a nutrient for plants and animals. 13, 27 The normal human dietary intake of zinc is about 10 to 15 mg. a day. The stool is the major excretory route; it contains about 10 mg. a day, whereas the urine contains only about 0.4 to 0.5 mg. a day.17 The amount of zinc in different human organs varies between 10 and 200 µg. per gram of wet tissue.30 The human liver contains 50 to 60 µg, of zinc per gram.34 The identification of zinc as a component of carbonic anhydrase was the first demonstration of its specific biochemical function.11 The role of zinc in metabolism has usually been interpreted solely in terms of its presence in this enzyme. Recent investigations in this laboratory, however, have demonstrated the presence of zinc in several dehydrogenases and in pancreatic carboxypeptidase. 37-40 Two of these enzymes, alcohol dehydrogenase and glutamic dehydrogenase, are isolated from mammalian liver.2, 21 Zinc is an active enzymatic site in these enzymes, and its presence is indispensable to their activity. 33, 35 Zinc is thus involved in the oxidation of ethanol, a substance that is considered to have a primary role in the development of some forms of Laennec's cirrhosis, 12 and in the faulty metabolism of ammonia in patients with cirrhosis.12 These circumstances suggested an investigation of the metabolism of this metal in patients with liver disease.41, 42

\* Received for publication January 16, 1959.

Presented at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, May 2, 1958.

From the Biophysics Research Laboratory and the Medical Clinic, Department of Medicine, Harvard Medical School and Peter Bent Brigham Hospital.

† Supported by the Lasdon Fund, the Hartford Fund, the Rockefeller Foundation and the Howard Hughes Medical Institute.

Requests for reprints should be addressed to Bert L. Vallee, M.D., Biophysics Research Laboratory of the Department of Medicine, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Massachusetts.

#### MATERIALS AND METHODS

The procedures for the analysis of zinc and the cleaning of glassware and containers have been described.<sup>7, 36</sup> De-ionized water was used throughout.

Analyses of Serum: Duplicate zinc analyses were performed on 2-ml. aliquots of serum from venous blood, obtained without regard to the fasting state. Blood was drawn into acid-cleaned sterile syringes through special stainless steel needles, transferred to acid-cleaned, dried Pyrex centrifuge tubes, allowed to clot, and centrifuged within an hour of collection.<sup>36</sup> The serum was decanted and stored in polyethylene tubes at 4° C. Contamination was not encountered in any of these steps.

The controls were eight normal females and 32 normal males, of ages between 20 and 51 years. Thirty-three patients with Laennee's cirrhosis, seven females and 26 males, constituted the experimental group. Their ages ranged from 29 to 82 years. A history of alcoholism or poor diet was regarded as a prerequisite to the diagnosis of Laennee's cirrhosis. The diagnosis was established by biopsy in three cases and by autopsy in three.

Analyses of Urine: Zinc analyses were performed on 5-ml. aliquots of 24-hour specimens which were collected directly into acid-cleaned polyethylene bottles to avoid contamination. Zinc was extracted directly from urine and measured as the zinc dithizonate, with a reproducibility indicated by a coefficient of variation of 2.1%.

Fourteen normal men, ranging in age from 21 to 38 years, served as controls for the study of the zinc content of urine. Nine male patients, ranging from 51 to 69 years of age, comprised the experimental group. All of these patients suffered from postalcoholic cirrhosis that was "severe" as judged by the previously published classification.<sup>42</sup>

Analyses of Liver: Liver samples obtained at autopsy were stored in the frozen state. Two sections, each weighing from 20 to 30 gm., were obtained from different parts of the liver. They were minced with a stainless-steel knife on a glass plate, dried at 95° C. to constant weight (48 hours), and then ashed in platinum dishes at 450° C. in a quartz-lined muffle furnace. Zinc, copper and all other metals present were determined by chemical or spectrographic methods, or both. The precision of these methods is high, providing a reliable measure of the alterations about to be described. <sup>6, 7, 10, 34, 36</sup> The calculation of metal content was based on the wet weight of tissue, the dry weight and the nitrogen content.

The metal contents of seven liver specimens obtained at postmortem examination were determined as controls. In none of these was there any histologic evidence of liver disease. The livers obtained at autopsy of four males and one female ranging in age from 39 to 82 years, all with histologically confirmed Laennec's cirrhosis, comprise the experimental series for the measurement of hepatic metal content.

#### RESULTS

Serum Zinc: The distribution of the average values from duplicate zinc determinations on the serums of 40 normal persons is shown in the proximal plane of figure 1. The mean is  $x_n = 120 \pm 19 \mu g$ , per 100 ml. A  $\chi^2$  test showed this to be consistent with the Gaussian distribution, as expected for a biologic sample of this type. Age, sex, food intake and diurnal variation were not found to be significant variables.

The distal plane of figure 1 shows the histogram for duplicate determinations of serum zinc in 25 patients of the severely cirrhotic group. The mean is  $\bar{x}_c = 66 \pm 19 \ \mu g$ . per 100 ml. This distribution also approximates the Gaussian distribution, as shown by the  $\chi^2$  test. The mean value is almost

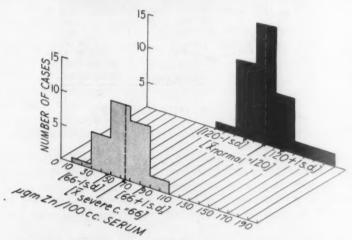


Fig. 1. Frequency distributions of serum zinc in 40 normal persons and 25 patients with severe cirrhosis. The mean ± 1 standard deviation is indicated for each group.

half that of the normal population. The standard deviation is identical with that observed for the normal group. The difference from the normal group is highly significant.

Patients classified as having "mild" cirrhosis by criteria described previously <sup>42</sup> had a mean serum zinc concentration  $x_m = 87.8 \pm 20 \mu g$ . per 100 ml. of serum. Compared with the normal group, the mean of this group is lower and the distribution is shifted to distinctly lower values, while the standard deviation is nearly identical.

Figure 2 shows the serum zinc concentrations and the clinical course of two patients with severe cirrhosis; both entered the hospital after prolonged alcoholic bouts. Case E. H. presented jaundice and vomiting, and case F. H. vomiting and delirium tremens, as the chief complaints. Both showed marked clinical improvement after two weeks of therapy in the hospital with

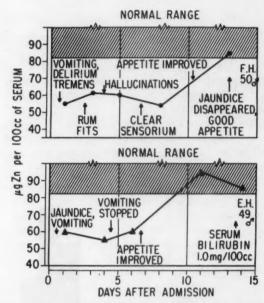


Fig. 2. Serum zinc concentrations of two patients with severe cirrhosis.

vitamins and a high calorie, high carbohydrate diet. The serum zinc concentration, low at the time of admission, rose progressively to higher levels concomitant with the patients' improvement.

Urinary Zinc Excretion: The 24-hour amounts of zinc excreted by nine patients with postalcoholic cirrhosis and the corresponding urine zinc con-

Table 1
Urine Zinc Content of Nine Patients with Postalcoholic Cirrhosis

Patient	μg. Zn/24 hrs.	μg. Zn/ml. Urine/24 hrs.	
I. O.	994	1.13	
F. H.	1396	.76	
B. T.	773	.82	
H. S	875	.69	
I. B.	1113	1.97	
I. R.	1256	.46	
I. G.	844	71	
T. S.	939	.70	
J. K.	1080	.64	
Mean	1030	.88	
Standard Deviation	188	.42	

centrations are shown in table 1. Zinc elimination is markedly increased in patients with cirrhosis, compared to the control group (table 2).

The zinc excretion, concentration of zinc in serum and liver function of six of these patients—B. T., figure 3, J. O., J. K. and J. G., figure 4, T. S.,

TABLE 2
Urine Zinc Content of 14 Normal Men

Name	μg. Zn/24 hrs.	μg. Zn/ml. Urine
P. R.	370	.21
C. P.	375	.29
I. M.	548	.93
R. T.	465	
I. K.	410	.43
W. W.	355	.34
E. R.	660	.66
M. M.	655	.64
F. H.	455	.25
S. A.	338	.55
T. C.	380	.31
R. D.	273	.14
P. S.	549	.44
J. L	559	.56
Mean	457	.44
Standard Deviation	120	.21

figure 5, and A. L., figure 6—were studied over a period of time. All were given zinc by mouth in physiologic quantities, supplied as capsules containing 30 mg. of zinc sulfate. Three of these were taken each day, a dosage equivalent to a total of 19.5 mg. of zinc per day, the approximate normal daily intake.

All patients studied exhibited subnormal concentrations of zinc in their serum; the magnitude of this reduction was a function of the severity of the disease.<sup>42</sup> With the exception of the one very advanced case in the group (A. L., figure 6), all of these patients reëstablished normal zinc excretion

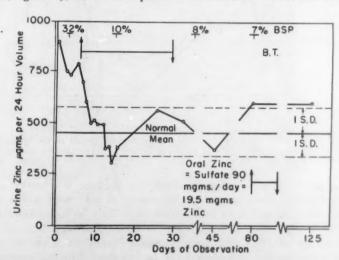


Fig. 3. Serial 24-hour total urinary zinc determination and bromsulfalein retention of a patient (B. T.) with known postalcoholic cirrhosis, shown in relation to the oral administration of zinc sulfate.

after zinc administration. However, the rate at which this change was achieved differed markedly, occurring after two days in B. T. and four weeks in T. S. The data imply that urinary zinc excretion in patients with moderately reversible disease decreases from very high concentrations to normal (J. K., figure 4) as the disease progresses, to become and remain extremely low once the process is completely irreversible (A. L., figure 6).

Functional Response: The degree of bromsulfalein retention has been shown to have excellent correlation with the clinical status, hepatic function and zinc metabolism in patients with postalcoholic cirrhosis. 42 In the

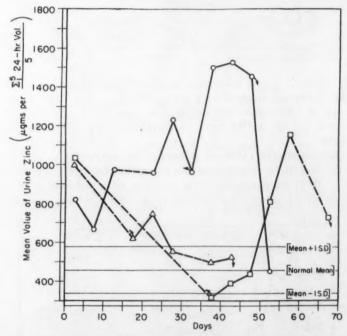


FIG. 4. Mean values taken over each successive five-day period of the total 24-hour urinary zinc excretions of three patients (J. K., J. O. and J. G.), shown in relation to the oral administration of zinc sulfate.

present group of patients, a distinct and lasting decrease in retention of the dye was observed when physiologic quantities of zinc were given orally (table 3): from 32 to 7% in B. T., from 34 to 23% in J. O., from 38 to 25% in T. S., from 27 to 19% in J. K., and from 47 to 36% in J. G.

In one case (B. T.), this decrease was followed for a period of six months (figure 3), and was observed to be sustained. In this patient, the first decrease occurred after as little as one week, but it was seen as late as the fourth week in J. O. (figure 4). The absolute magnitude and the rate

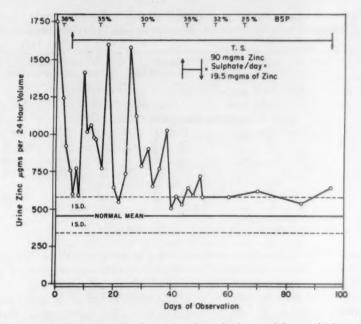


Fig. 5. Serial 24-hour total urinary zinc determinations and bromsulfalein retention of a patient (T. S.) with known postalcoholic cirrhosis, shown in relation to the oral administration of zinc sulfate.

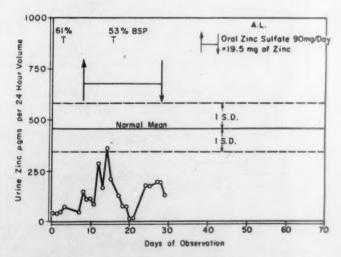


Fig. 6. Serial 24-hour total zinc determinations and 45-minute bromsulfalein retention of a patient (A. L.) in the terminal stages of postalcoholic cirrhosis, shown in relation to the oral administration of zinc sulfate.

TABLE 3

Bromsulfalein Retention, Serum Zinc Concentration, and Urine Zinc Content of Seven Patients Before and After the Administration of Zinc Sulfate

Patient	BSP Retention		Serum Zinc µg./100 ml.		Urine Zinc Content µg./24-hour Volume	
	. А	В*	A	В	Α .	В
		Patients wit	th Postalcoho	lic Cirrhosis		
B. T.	32%	7%	72	78	773	439
I.O.	34%	23%	85	88	994	515
T. S.	38%	25%	66	61	939	630
I. K.	27%	19%	74	84	1080	727
J. G.	47%	36%	64	67	844	444
	Pa	tient with Ter	minal Postal	coholic Cirrh	osis	
A. L.	61%	53%	49	36	1 44 1	125

\* A = Prior to zinc administration.

B = Last determination in the course of zinc administration.

of change differed considerably among these patients, as did the biology of their disease. There had been no evidence of spontaneous recovery of liver function in any of these cases prior to these studies.

Most of the patients received a normal hospital diet while under study, estimated to contain 15 mg. of zinc per day. No other special dietary

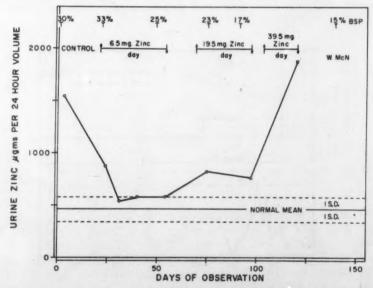


Fig. 7. Serial 24-hour total urinary zinc determinations and bromsulfalein retention of a patient (W. McN.) with known postalcoholic cirrhosis, shown in relation to the oral administration of zinc sulfate.

measures were instituted, and therapy was otherwise symptomatic except that two patients, A. L. and J. G., were taking diets low in protein while under observation.

In one patient (W. McN.), the amount of oral zinc was varied (figure 7). Zincuria diminished coincident with an oral intake of 6.5 mg. of zinc per day; the normal urine zinc excretion was maintained on 19 mg. per day. Zincuria appeared promptly, however, when the oral intake was raised to 39 mg. of zinc per day, even though the bromsulfalein retention had decreased from 33% to 15% over the 100 days of zinc administration, and the serum zinc was within the normal range.

Metal Content of Liver: Liver samples obtained at autopsy from five persons who succumbed to postalcoholic cirrhosis, and from seven persons dying without evidence of cirrhosis, were analyzed for zinc, iron, calcium,

Table 4

Emission Spectrographic and Microchemical Determinations of Metals in Livers of Autopsied Patients With and Without Postalcoholic Cirrhosis

Element	Noncirrhotic	Cirrhotic	Noncirrhotic	Cirrhotic	Noncirrhotic	Cirrhotic
Liement	μg. metal/g	m. wet wt.	μg. metal/g	gm. dry wt.	μg. meta	al/mg. N
Zinc	69±23 74±23(a)	29±8 29±7(a)	288±100 311±100(a)	99±37 100±30(a)	2.8±.29 2.9±.9(a)	1.4±.42 1.4±.29(a)
Calcium	30±7	34±12	126±30	118±50	1.2±.4	1.7±.9
Iron*	223±111	38±17	$934 \pm 470$	132±86	$10.9 \pm 3.8$	1.0±.57
Manganese	1.3±.3	$1.7 \pm .56$	$5.2 \pm 1.4$	$5.0 \pm 1.1$	$.05 \pm .01$	$.08 \pm .04$
Aluminum	.85±.3	.69±.5	$3.6 \pm 1.2$	$6.5 \pm 2.6$	$.03 \pm .01$	$.03 \pm .02$
Magnesium	128±44	$103 \pm 23$	531±159	$362 \pm 162$	$5.0 \pm 1.2$	$5.1 \pm 2.4$
Copper	$5.3 \pm 1.3(b)$	$6.8 \pm 2.6 (b)$	22±5.1(b)	24±11(b)	.21±.08	$.34 \pm .2(b)$

a = Chemical analysis (36).

magnesium, manganese and copper (table 4). Zinc and iron are significantly decreased in cirrhotic livers independently of the parameter chosen to express metal content: wet or dry weight, or nitrogen content. Other workers have made similar observations.<sup>16</sup>

The wide range of the iron content may reflect the variable blood content of the specimens. There were no corresponding changes in the content of any of the other elements measured, lending further emphasis to the data on zinc and iron.

#### DISCUSSION

The data presented indicate that the serum zinc concentration is decreased in Laennec's cirrhosis. The lowest serum zinc level obtained in these studies —20 µg. per 100 ml.—was measured in a patient who was in deep and fatal

b = Chemical analysis (6).

<sup>\* =</sup> Probable contamination of sample with blood.

hepatic coma. Urinary zinc excretion is increased similarly in this disease. The degree both of elevation of urinary zinc and of lowering of serum zinc correlates with the severity of the disease.

The administration of physiologic amounts of zinc sulfate to patients with postalcoholic cirrhosis results in a return to normal of the abnormal zinc metabolism. In one instance (W. McN.), an increase of the oral zinc intake from 19.5 to 39 mg./day caused an immediate rise in urinary zinc excretion. It is thus evident that the amount of oral zinc which is administered is an important parameter in regard to the effect of this element on zincuria. When this patient was given 6.5 or 19.5 mg. a day zincuria disappeared; when the intake was raised to 39 mg. a day zincuria promptly recurred, suggesting that the observed zincuria is a critical function of zinc available to the organism.

Changes in the serum and urine zinc concentrations may also be indices of changes in hepatic function: both urinary zinc and serum zinc return to normal concomitant with clinical improvement.

In these patients the lowered serum zinc concentrations seemed to bear a relation to bromsulfalein retention. This relation was not found to prevail in patients with liver disease other than postalcoholic cirrhosis. It appears at present that the lowered serum zinc concentration is more consistently observed in patients with Laennec's cirrhosis than in other instances of liver disease. Determinations on the serums of eight patients with infectious hepatitis gave a mean serum zinc concentration of  $107 \pm 25.4 \, \mu g$ . per  $100 \, \text{ml}$ . The range was  $73 \, \text{to} \, 165 \, \mu g$ . per  $100 \, \text{ml}$ . This series is small, but the difference from the normal group is not striking.

The low concentrations of zinc and iron in serum <sup>5</sup> are accompanied by significant diminutions of the concentrations of these elements in cirrhotic livers. A further deviation in zinc metabolism is indicated by the marked zincuria in patients who have not reached the terminal stages of postalcoholic cirrhosis.

These marked alterations of zinc metabolism were sought as a result of the discovery of zinc metalloenzymes in liver tissue, and must be considered in the context of existent knowledge concerning postalcoholic cirrhosis, but also they must be considered in terms of the biochemistry of zinc, a factor which has not previously been known to be pertinent.

It may be of some interest in this regard that zinc has long been employed as an effective remedy against infantile hepatic necrosis in India. No statistical, chemical or reliable clinical data are available to evaluate the effectiveness of this procedure. However, zinc oxide has been given therapeutically by Prabhu <sup>23</sup> with "very gratifying results" both in arresting the progression of the disease and in advanced cases. The metal was employed based on the use of a popular, indigenous preparation. The very high incidence of infantile cirrhosis in Hindu Brahmin children, who are on characteristically restricted diets, had suggested a nutritional basis.

calcium.

The low zinc contents of serum and of liver are most readily explained by a deficiency of zinc. This could arise from an inadequate intake as a primary cause, a possibility that cannot be excluded in view of the dietary habit patterns of alcoholic patients. The simultaneous existence of zincuria, however, raises the question of the existence of a conditioned deficiency, in which the normal intake of the nutrient does not meet the needs of the organism owing to the presence of unusual, secondary circumstances or factors.18 The "conditioning factors" for many nutrients have been described fully and require no elaboration. 27, 28 The consequences of conditioned deficiencies are indistinguishable from those due to inadequate intake but they are differentiated by the mechanism of their production. Porcine parakeratosis, an endemic zinc deficiency, serves as an example.

Parakeratosis can be induced in swine purely by an insufficient dietary intake of zinc. It may also be brought about by high levels of calcium in the diet, in the presence of zinc sufficient to support normal growth and development in the absence of high calcium. High calcium content of the forage is the "conditioning factor" that brings about "zinc-deficiency disease" in a manner that is not understood at present. Increasing the amounts of zinc beyond the normal requirement protects the animals against the effect of calcium. 8, 14, 15, 28 Preliminary observations 32 indicate changes in enzymatic activities of dehydrogenases in the livers of young pigs receiving diets varying in calcium and zinc content. A decrease of alcohol and glutamic dehydrogenase activities seems related to intake of high levels of

Factorial design in nutritional animal experimentation readily demonstrates such nutritional or metabolic interactions, and hence many examples of this type are known for plants and animals.29 It is much more difficult to identify conditioning factors in man, both because of his social habits and because of the obvious limitations imposed in experimentation. It does not seem reasonable to suppose that the changes in zinc metabolism observed in patients with postalcoholic cirrhosis would be the result of primary zinc deficiency alone. Zincuria, caused by whatever metabolic abnormality, could certainly deplete the zinc stores of the body so that inadequate amounts of zinc would be available for cellular functions, even if the intake were normal.

The alterations in liver zinc and iron contents, two elements of crucial significance in oxidative catalysis, point to the metalloenzymes of these elements 30 as possible loci of such a biochemical defect. While separate study is necessary to assess the role of iron in this disease, the participation of zinc in the dehydrogenation of ethanol 37, 38 and of glutamic acid, 33 two substrates that are clearly implicated in the metabolic changes accompanying cirrhosis, enhances this view. Although the features of either a primary or a conditioned zinc deficiency in man have never been described, zinc is present in all phyla and species, and participates in the dehydrogenation of ethanol and other enzymatic processes in widely diverse living forms. Transphylar analogies thus seem permissible for the purpose of predicting at least the areas of metabolism that might be affected by defects in zinc metabolism in man. Similar analogies have been shown to be valid by the comparable effects of deficiencies of other metals in lower and higher forms of life.<sup>29</sup>

In Neurospora crassa and in the pig, zinc deficiency has been shown to result in disturbances of protein balance. In Neurospora, ethanol detoxification is completely destroyed, 19, 20 while this system may show only relative diminution in the zinc-deficient swine. The biochemical alterations are the more easily discernible the lower the organizational level of the experimental subject examined. The complexity of the mammal precludes the localization of a biochemical lesion with facility equal to that encountered in lower forms of life, although deductions about the site of such lesions may be drawn by analogy. Therefore, some further details of the comparative biochemistry of ethanol metabolism may prove to be germane to the study of zinc metabolism in cirrhosis.

The lowest evolutionary forms adapt very well to the presence of ethanol; certain yeasts have developed metabolic patterns in which their alcohol dehydrogenase is involved in ethanol production. In the mammal, the reverse reaction is favored, presumably. The liver of the horse contains alcohol dehydrogenase as 1% of its total protein content.<sup>26</sup>

Horse-liver alcohol dehydrogenase is the only mammalian ethanol oxidase so far available for study. Although zinc has a role in ethanol oxidation in the horse and in a variety of organisms, the details of its function in this process and in the molecular structure of the catalyst have apparently become modified by evolution. The pure yeast enzyme, for example, oxidizes ethanol approximately 200 times faster than does the pure mammalian enzyme. Beyond this, the mammalian enzyme has gained the capacity to oxidize other alcohols, among which are glycerol and vitamin A<sub>1</sub>. Liver alcohol dehydrogenase thereby affects several additional metabolic pathways, and interference with this enzyme will have more widespread effects.

With these considerations in mind it is possible, in fact, to reinterpret previous studies in man and to relate them to these analogies. A vitamin A deficiency manifested by defective dark adaptation was found to be resistant to administration of the vitamin in patients with cirrhosis.<sup>22</sup> Vitamin A<sub>1</sub> alcohol dehydrogenase and liver alcohol dehydrogenase appear to be the same enzyme,<sup>1</sup> which contains 0.18% of zinc.<sup>38</sup> Zinc has long been known to be present in the retina of many species in high concentrations.<sup>3</sup> A resistant deficiency of vitamin A exists in porcine parakeratosis.<sup>25</sup> These studies of dark adaptation in human postalcoholic cirrhosis therefore seem to reflect the altered zinc metabolism in this disease.

Thus, the analogies of zinc and ethanol metabolism in microörganisms and mammals may be valid also in the human being. Such an organism as

Neurospora does not show the anatomic consequence of a metabolic lesion, but the lesion itself is more easily discernible. These studies focus on a specific area of metabolism and a metabolic component, zinc, through which a different approach to this prevalent human disease may be obtained.

## SUMMARY AND CONCLUSIONS

Marked abnormalities of zinc metabolism are demonstrated in patients suffering from postalcoholic cirrhosis. Zinc concentrations in serum and in the liver tissue of such persons are markedly lowered. Simultaneously, these patients excrete abnormally large quantities of zinc in their urine; a terminal patient, however, excreted abnormally low quantities of zinc. The administration of zinc sulfate in physiologic quantities tends to restore normal excretory patterns. The bromsulfalein retention in five patients with postalcoholic cirrhosis tended toward normal in the course of these investigations on zinc metabolism. No attempts at specific therapy of the disease were undertaken.

The data are interpreted in the light of the comparative biochemistry of zinc and ethanol metabolism. A conditioned zinc deficiency is conjectured to be consistent with the present data and the known historical, pathophysiologic and pathobiochemical knowledge of this disease.

### SUMMARIO IN INTERLINGUA

Marcate anormalitates del metabolismo de zinc es demonstrate in patientes suffrente de cirrhosis postalcoholic. Le concentrationes de zinc in le sero e in le histos hepatic de tal personas es marcatemente reducite. Simultaneemente, iste patientes excerne anormalmente grande quantitates de zinc in lor urina. Tamen, in un caso—illo de un patiente terminal—un excretion anormalmente basse de zinc in quantitates physiologic tende a restaurar un normal situation excretori. Le retention de bromsulfaleina in cinque patientes con cirrhosis postalcoholic tendeva verso valores normal in le curso de iste investigationes del metabolismo de zinc. Nulle essayos de trovar un therapia specific del morbo esseva interprendite. Le datos es interpretate in le lumine del biochimia comparative del metabolismo de zinc e de ethanol. Es conjecturate que un conditionate carentia de zinc es compatibile con le presente datos e etiam con le currente cognoscentias historic, pathophysiologic, e pathobiochimic relative a iste morbo.

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# THE PHYSIOLOGIC BASIS FOR VASOPRESSOR THERAPY DURING SHOCK \*

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## INTRODUCTION

THE therapeutic usefulness of vasopressor agents, although employed many years for correction of various shock syndromes, remains highly controversial. Some investigators disapprove of their indiscriminate use;1-3 others have advocated such therapy routinely.4,5 The basis for the divergence of opinion may be traced to variation in interpretation of the clinical Conclusions favoring the routine employment of vasopressor therapy often fail to consider that: (1) improvement of the systemic arterial blood pressure is not synonymous with therapeutic benefit; in some instances "cures" have been ascribed to vasopressor drugs although the ultimate outcome was fatal; (2) lessening of cyanosis, though generally a favorable sign, actually may connote further tissue ischemia, rather than improved blood flow; (3) the clinical studies include inadequate numbers of untreated control patients comparable with respect to severity of shock and underlying physiologic status; the survival of a previously healthy young male treated with vasopressor agents and the death of an elderly, emaciated male without such therapy, though both exhibit shock of similar intensity and etiology, do not prove the value of the therapy; (4) the difficulty in evaluation of the severity of shock leads to inaccuracy in appraisal of any form of therapy: (5) studies which fail to identify the precipitating factor and the duration of shock are virtually meaningless, since the precipitating factor and the time factor determine the potential value of vasopressor drugs; (6) certain supplemental forms of treatment, usually regarded as unimportant, may influence markedly the outcome of shock. Isotonic saline infusions per se (often the vehicle for the vasopressor agent) are as valuable as colloidal solutions for treatment of shock syndromes associated with plasma loss. 6, 7

Rather than attempt to determine the efficacy of vasopressor therapy from the numerous uncontrolled clinical reports, the present review considers the mechanisms of action of vasopressor drugs in relation to certain physiologic derangements of the peripheral vascular system during the various shock syndromes. Although in many instances the data are limited to animal experimentation and further clinical evaluation is required, a rational

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basis for the employment of vasopressor therapy becomes evident. This approach also permits a critical analysis of the results of pertinent clinical and experimental studies.

## PHYSIOLOGIC BASIS OF SHOCK

Shock has been accepted as peripheral circulatory failure resulting from a discrepancy between the size of the vascular bed and the volume of intravascular fluid.8-10 Shock persisting despite restoration of the blood volume is then attributed to an "increased capacity" of the vascular reservoir. This concept is inaccurate. The capacity of the normal mammalian vascular system is always greater than the blood volume contained therein. Moreover, in the normal state, as well as during shock, the capacity of the vascular bed in any particular subject remains constant. It is not the size of the vascular reservoir, but rather the size of the entrance to a segment of the vascular reservoir—the capillary bed—that is one crucial factor in determining the outcome of the shock state. The capillary entrance size determines whether blood bypasses the capillary bed via the larger arteriovenous thoroughfare channels, or floods this vascular area. The capillary inlet is guarded by a complex arrangement of peripheral vasomotor mechanisms which, functioning as physiologic stopcocks, continuously restrict blood flow to varying extents through the minute vessels of all tissues. This continuous stopcock activity, by preventing the entire capillary bed from filling simultaneously, supports the effective containment of the blood volume in the central vascular reservoir.

As a consequence of vascular capacity exceeding total blood volume, the normal organism fluctuates in a precarious state. Circulatory homeostasis is continuously dependent upon the ability of peripheral vasomotor activity not only to maintain an acceptable degree of ischemia through the minute vascular bed in all tissues, but also to promote increased blood flow to one area while simultaneously and proportionately increasing ischemia in others. This integration is definitely advantageous under normal conditions. It permits efficient utilization of a relatively small quantity of blood so that the myocardial work otherwise required to pump blood through a totally filled vascular system is reduced markedly. The sacrifice for this myocardial security is peripheral vascular insecurity. Whenever the relatively small quantity of circulating fluid volume is reduced further, or when generalized failure of the vasomotor mechanism ensues, with flooding of the capillary bed and decrease in effective circulating blood volume, tissue blood flow is decreased and shock, which is normally latent, becomes clinically apparent. Despite the presence of an intact circulatory volume and peripheral vasomotor system, if the myocardium fails to maintain an adequate output, tissue blood flow also decreases. When cardiac output falls gradually and there is sufficient time for the blood volume to increase, the augmented filling of the

TABLE 1

Precipitating Mechanisms of Shock Syndromes

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Myocardial infarction

Asystole

Severe and sustained tachycardia

Acute congestive heart failure

Valvular stenosis with mild tachycardia

Cardiac trauma

Terminal congestive heart failure

Aortic or pulmonary artery thrombosis

Acute cardiac tamponade

### Periphera

I. Loss of Blood Volume

Hemorrhage Plasma loss (trauma) Dehydration

## II. Loss of Vasomotor Function

### A. Arteriolar

Orthostatic Anesthesia Drugs Fever

Acidosis Hyponatremia

Injury to medullary vasomotor center Postoperative pheochromocytoma

## B. Capillary

Infection Anaphylaxis Toxins Hepatic failure Adrenal failure

## DIFFUSE CAPILLARY INJURY INVOLVING THE MYOCARDIAL ←—— CAPILLARY BED

vascular reservoir in the presence of an intact vasomotor system permits arterial blood pressure to be maintained despite tissue ischemia. When cardiac output falls so rapidly that compensatory increase in blood volume is inadequate, the more typical shock syndrome ensues.

The lesions capable of *precipitating* the shock syndrome are varied (table 1). Peripheral circulatory failure may be initiated by loss of fluid volume or by loss of vasomotor function. Loss of vasomotor function may become manifest primarily at the arteriolar level, or in the smaller tributaries of the arterial tree. This distinction, to be described subsequently, is of fundamental importance. Present evidence suggests that traumatic shock is not a unique form of peripheral circulatory failure, but develops largely as a sequel to plasma loss from the injured capillary bed at the traumatized site.<sup>11, 12</sup>

Once initiated, regardless of etiology, additional factors perpetuate the shock syndrome and lead eventually to a phase characterized as therapeutically "irreversible." Although the physiologic basis for the irreversible state is incompletely defined, progressive and generalized pooling of blood within the capillary reservoir appears to be one basic contributory peripheral mechanism. Schematically, the capillary bed is represented by figure 1; variations of this structure are related to varying tissue functions. A significant feature is the presence of two "circuits." The first, indicated as circuit 1, is a direct shunt from arteriole to venule. Arising therefrom as lateral tributaries, circuit 2 supplies the true capillary bed. The amount

<sup>\*</sup>Failure of venomotor mechanisms with venous pooling of blood has recently been implicated as another important contributory peripheral mechanism.<sup>10</sup>

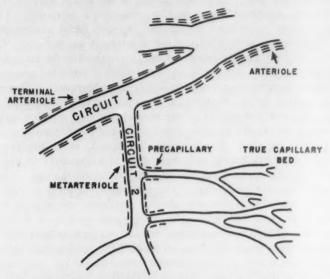


Fig. 1. Schematic representation of the capillary vascular bed. (Modified from Zweifach.<sup>140</sup>)

of blood permitted to flow through this second circuit is normally regulated carefully by the caliber of the metarterioles and the precapillary sphincters. These vessels are continuously active, undergoing intermittent and independent constriction and dilatation for immediate adjustment of local tissue demands for capillary blood flow. This process of "vasomotion," considered collectively, directly determines the total quantity of blood permitted to enter the true capillary bed. 17, 18 The caliber of the arterioles is normally influenced by both humoral and neurogenic control, whereas capillary vasomotion is influenced primarily by humoral factors and by the concentration of locally released tissue metabolites. 18, 19 The peripheral vasomotor apparatus thus comprises a dual system-metarteriolar and precapillary vasomotion, constituting the fine adjustment for regulation of tissue blood flow, and variations in arteriolar caliber, constituting the coarse adjustment. Normally, both processes are integrated to restrict blood flow continuously to all tissues to varying degrees. Physiologic restriction of tissue blood flow by the metarterioles and precapillary sphincters may be viewed as the first line of defense, and that by the arterioles as the second line of defense, in preventing the circulating blood volume from entering, passively distending, and being sequestered within the true capillary bed.

Generalized failure of the first line of defense is catastrophic. Even in the presence of intense arteriolar constriction, when capillary vasomotion is impaired (manifested by an increase in duration and frequency of metarteriolar and precapillary dilatation), progressively larger quantities of blood

enter the capillary area. The total volume of blood that may be contained in the passively congested human capillary reservoir is unknown. The most definitive attempt to estimate mammalian capillary blood volume was performed by Gibson et al.20 Utilizing radioisotopes in normal dogs, they concluded that 17% of the total blood volume is contained in the minute vessels. The accuracy of this conclusion is open to question, since the measurements were obtained in animals sacrificed by intravenous Nembutal. This manipulation, as judged by observations of the rat meso-appendix, may lead to severe postmortem terminal arteriolar constriction and capillary ischemia.<sup>21</sup> Consequently, the normal capillary blood volume of the dog may significantly exceed 17% of the total. Furthermore, the capacity of the capillary bed to be distended passively during pathologic states is so marked that many times the normal capillary blood volume may be contained therein. Wiggers 22 has summarized this impression: "There seems to be no question but that during this stage [of irreversible shock] capillaries are able to hold unbelievably large quantities of blood." Progressive pooling of blood in such an expansile capillary reservoir could account, at least in part, for the development of the irreversible phase of shock.23,24 Studies have shown that this mechanism occurs as experimental hemorrhagic or traumatic shock progresses, and that the deterioration of capillary vasomotion can be correlated with the degree of irreversibility of the shock syndrome. 25-30 Moreover, related studies with radioisotopes demonstrate widespread trapping of blood in the minute vessels of all tissues, including the spleen, liver, kidneys, heart, intestine, muscles and brain. 31 There appears to be a critical point of blood loss above which trapping of red cells develops; in anesthetized dogs this occurs after a bleedout of between 26 and 38% of the initial blood volume.82 That pooling of blood in the capillary bed is not the sole factor leading to the irreversibility of low blood volume shock syndromes is perhaps best illustrated by the finding that only a fraction (15 to 50%) of the total blood volume need be trapped in the minute vascular bed before the irreversible phase is demonstrable.81

# Effect of Vasopressor Agents on the Peripheral Vasomotor System During Shock

Normally, the precapillary sphincters and metarterioles are more reactive to either topical or circulating vasopressor agents than are other elements of the vascular system. Intravenous infusions of norepinephrine into human subjects in low concentrations increase the frequency and duration of the constrictor phase of vasomotion of the nailfold capillary bed before producing arteriolar constriction sufficient to elevate systemic arterial blood pressure. A gradient of responsiveness to pressor substances exists, with the reactivity of the precapillary, metarteriole and arteriole decreasing in that order. During the early phase of hemorrhagic and traumatic shock this gradient is maintained; as shock progresses, reversal of the gradient develops. The

sensitive precapillary sphincters and metarterioles appear to be highly susceptible to anoxia and/or other noxious stimuli. It is stressed that these findings have thus far been confirmed only in the mesenteric capillary vascular area of the experimental animal. Nevertheless, reversal of the responsiveness gradient may be a key factor in determining the diminished effectiveness of vasopressor agents during the latter phases of shock. Under normal conditions, or during the early phases of low blood volume shock, the administration of vasopressor agents restricts blood from entering the capillary bed. Blood is not only shunted to larger vessels, but resorption of interstitial fluid is also favored by this alteration in capillary dynamics. Venous return, and therefore cardiac output, are increased. As shock progresses, vasopressor agents may intensify arteriolar constriction in certain areas, but would be unable to enhance the impaired capillary vasomotor activity. Blood continues to pool in the capillary bed, and venous return is no longer increased appreciably.

# MECHANISMS FOR CAPILLARY VASCULAR REFRACTORINESS TO VASOPRESSOR AGENTS DURING LOW BLOOD VOLUME SHOCK

Although progressive impairment of capillary vasomotion and reactivity to vasopressor agents evolve as low blood volume shock persists, certainly, at least in the mesenteric area, the mechanisms responsible are poorly defined. Hypoxia, ill defined toxins resulting from tissue anoxia, and arteriolar

constriction may be contributing factors.

1. Hypoxia. Prolonged lowering of arterial oxygen content secondary to decreased oxygen-carrying capacity in hemorrhagic shock or pulmonary congestion following myocardial failure is probably a contributing factor in the evolution of impaired capillary vasomotion and refractoriness to vasopressor agents. The microscopic erythrocytic emboli which appear after trauma—"sludged blood" blood" accompanged exchange, and may thereby lead to reduced capillary responsiveness. The hemoconcentration and increased blood viscosity which accompany shock of traumatic or other origin may also impede capillary blood flow and eventually interfere with capillary vasomotion and reactivity. Conceivably, this explains the observation that shock secondary to loss of plasma volume is more poorly tolerated than is that due to loss of equal volumes of whole blood. Box of the myocardium could contribute to myocardial insufficiency and perpetuate the hypoxic state.

2. Toxic Humoral Factors. The role of humoral toxic factors in the pathogenesis of impaired capillary vasomotion and refractoriness to vasopressor agents during low blood volume shock remains speculative. The significance of elevated serum ammonia levels <sup>37</sup> requires evaluation, since the ammonium ion is a potent inhibitor of capillary vasomotion. <sup>38</sup> The contribution of "VDM," a substance which impairs rat meso-appendiceal capillary vasomotion and responsiveness to epinephrine, identified as ferritin and

postulated to be of basic importance in the development and maintenance of irreversible low blood volume shock, 13, 26, 39, 40 now appears to have little significance as evaluated in the experimental animal. 41-45 Although the intravenous injection of purified horse spleen ferritin \* into six human subjects in amounts ranging from 2 to 300 micrograms ferritin N/Kg. consistently failed to alter arterial blood pressure, pulse rate, or threshold reactivity of the bulbar conjunctiva or nailfold capillary bed to epinephrine, 46 it is possible that capillary reactivity was depressed in the mesenteric area. However, the concept that VDM may play a role in human shock (or other illnesses) requires reëvaluation in terms of the ability of normal human plasma to depress the epinephrine reactivity of the rat meso-appendiceal capillary vascular bed. 47 During the course of traumatic shock, noxious substances may be released directly from injured tissues. One group of substances, the thromboplastic factors, is composed of potent capillary dilator agents: 48 the intravenous injection of thrombin in small quantities (8 units/ 100 gm.) sharply depresses the epinephrine reactivity of the capillary bed of the rat meso-appendix.40

The role of intestinal-absorbed bacterial endotoxins in the pathogenesis of irreversibility of prolonged low blood volume shock is gaining increasing attention. Endotoxins can markedly affect capillary vascular reactivity to vasopressor agents. The injection of lethal quantities of bacterial endotoxin results in a transient hyperreactivity, followed by a profound refractoriness of the rat meso-appendiceal capillary bed. 50, 51 The concept that bacterial endotoxin participates in the irreversible phase of low blood volume shock is supported by the following observations: (1) Antibiotics, even those "nonabsorbable," administered to animals prior to hemorrhagic shock, reduce the mortality rate significantly. 52, 53 (2) The tolerance to bacterial endotoxin during the initial several hours following hemorrhagic shock, at least in the rabbit, is so altered that a dose 1/100,000 of that required to kill the normal animal may prove lethal.<sup>54</sup> (3) The perfusion of blood through the superior mesenteric artery of dogs under normal pressure and flow rates prevents prolonged hemorrhagic shock from becoming irreversible.<sup>55</sup> Such beneficial effects cannot be ascribed to increased hepatic blood flow, since similar results were obtained in dogs with chronic Eck's fistulae.55 (4) Rats rendered tolerant to bacterial endotoxin become highly resistant to drum trauma and hemorrhagic shock.<sup>56</sup> (5) The initial hyperreactivity and subsequent depression of the rat meso-appendiceal capillary bed to epinephrine induced by lethal doses of endotoxin resemble the vascular reaction seen during traumatic and hemorrhagic shock.<sup>56</sup> (6) Blood obtained from dogs during prolonged, severe hemorrhagic shock is lethal when transfused into dogs subjected to two hours of hemorrhagic shock. If, however, the donor dogs are treated orally with nonabsorbable antibiotics prior to the prolonged hemorrhagic shock, the lethal effect of their blood is decreased significantly.

<sup>\*</sup> Supplied through the courtesy of Dr. Ephraim Shorr (deceased).

Comparable results occur in the rabbit.<sup>57</sup> (7) Substances with certain of the properties of bacterial endotoxin have been demonstrated in the blood of

animals during prolonged hemorrhagic shock.58

Intestinal-absorbed bacterial endotoxin, however, cannot at present be unquestionably accepted as an essential factor in the pathogenesis of the irreversible phase of low blood volume shock. Thus irreversible shock can be produced in germ-free as readily as in ordinary rats subjected to graded hemorrhage; <sup>59</sup> enhancement of rat resistance to traumatic shock that follows repeated exposure to sublethal drum trauma fails to enhance resistance to the lethal action of bacterial endotoxin, <sup>50</sup> and studies in dogs that employ radioactive chromium-tagged *Escherichia coli* endotoxin indicate that intestinal adsorbed endotoxin could not account for the irreversible phase of hemorrhagic shock. <sup>60</sup> Recently, substances chemically related to bacterial endotoxins have been extracted from normal animal tissues. <sup>61</sup> Since these substances possess physiologic activity similar to that of bacterial endotoxins, it is possible that release of such material from injured cells contributes significantly to the development of capillary vascular refractoriness to vasopressor agents during the shock syndrome. <sup>61</sup>

The mechanism whereby lethal doses of endotoxin injure the capillary vascular system and lead eventually to refractoriness to vasopressor agents is unclear. Clues may be inherent in some recent studies indicating that endotoxin can alter vascular reactivity to epinephrine and norepinephrine in such manner that these hormones may then act as potent capillary necrotizing agents. <sup>62</sup> Moreover, reduction in capillary blood flow is produced by the intense and prolonged arteriolar constriction that follows the intravenous injection of endotoxin <sup>63</sup> which, together with the resulting constriction of the venules, at least in the mesenteric area, impedes capillary outflow and

favors pooling of blood and hypoxia of the capillary bed. 50, 51

3. Arteriolar Constriction. Although the parenchyma of certain tissues may withstand hypoxia for relatively long periods without irreversible damage, the regional capillary vascular bed exhibits signs of injury. The superimposition of prolonged arteriolar constriction upon the lowered perfusion pressure during shock severely accentuates this process. While arteriolar constriction is maintained by neurogenic mechanisms until the terminal phase of shock,64,65 possibly augmented by the action of bacterial and tissue endotoxins and endogenous pressor substances, 66 progressive capillary dilatation and refractoriness to vasopressor drugs result. A prototype of this reaction in man is observed readily in the nailfold capillary bed during the local arteriolar constriction of Raynaud's disease. As capillary blood flow is reduced or obliterated, vasomotion is progressively impaired and the capillary bed becomes increasingly congested and refractory to norepinephrine. 67, 68. The noxious effect of generalized intense vasoconstriction has been studied in normal dogs by infusing norepinephrine intravenously under light pentobarbital anesthesia. 69 When dosages of 2.0 gamma/kg./

min. for four hours were utilized, nine of 11 dogs died within 60 hours. The outstanding postmortem findings were extravasated blood in the intestinal lumen and extensive hemorrhagic foci in the lung.

Reduction in intestinal blood flow may play a major role in the pathogenesis of irreversible low blood volume shock, as indicated by the experiments on superior mesenteric artery perfusion cited previously. 55 More recent studies on thoracic aorta occlusion further suggest the importance of intestinal ischemia in the development of deterioration of cardiovascular function.70 Although reduction in intestinal blood flow following hemorrhage is due largely to the fall in systemic arterial blood pressure, a portion of the reduction is secondary to increased mesenteric vascular resistance.<sup>71</sup> Whether the noxious effect of reduced mesenteric blood flow is related to facilitation of intestinal absorption of bacterial endotoxins, to the elaboration of undefined toxic principles, or to pooling of blood within the mesenteric capillary bed as a result of impairment of capillary vasomotor activity combined with venous constriction 72 and increased resistance to portal outflow of blood 71 remains to be evaluated. The latter factor (pooling of blood) does not appear to be the essential one, since recent studies in the dog indicate that intestinal trapping of blood during advanced hemorrhagic shock is generally insufficient to account for irreversibility. 73, 74 Further data defining the precise role of intestinal ischemia in the development of epinephrine refractoriness of the mesenteric capillary bed and of irreversibility during low blood volume shock are urgently required.

If the irreversible state of low blood volume shock is indeed associated with sufficient injury to impair capillary vasomotion and responsiveness to vasopressor drugs, an increase in capillary permeability should be demonstrable. However, several investigators have demonstrated that, excluding the site of trauma, leakage of intravascular fluid is not increased during the latter stages of hemorrhagic or traumatic shock. 75-78 These findings have often been interpreted as synonymous with an absence of a generalized increase in capillary permeability. Such an interpretation would cast doubt on the occurrence of diffuse capillary vascular injury. Nevertheless, in the later stages of shock, with lowered systemic arterial blood pressure plus generalized and severe arteriolar constriction, mean capillary blood pressure must be reduced severely. Although capillary permeability may be markedly increased, this increase would be masked by the reduction in capillary blood pressure. 79 Only after capillary blood pressure rises following elevation of systemic arterial blood pressure and reduction of peripheral arteriolar constriction resulting from fluid replacement would a defect in capillary permeability be detectable. That this occurs in the dog is suggested by the appearance of hemoconcentration following blood replacement during the irreversible phase of hemorrhage shock.80 Although the quantity of plasma thus lost appears to be insufficient to account for irreversibility, 76 the noxious effect of tissue edema has not been excluded. Relatively small leakage of

plasma into crucial areas might impair function of vital organs sufficiently to contribute to irreversibility despite the insignificant decline in intravascular fluid volume.

## SHOCK SYNDROMES PRECIPITATED BY LOSS OF VASOMOTOR FUNCTION

In shock precipitated by conditions which directly impair capillary vasomotion (infection, 1 anaphylaxis, 2 toxemia, 2 or hepatic or adrenal failure 4 or hepatic or adrenal failure stages of low blood volume shock. The first line of defense has failed, the reactivity of the precapillary and metarteriole sphincters to vasopressor drugs is usually impaired, and venous return and cardiac output fall as blood pools within the minute vascular bed. The capillary bed of the myocardium probably shares in the injury incurred during these states, resulting in myocardial insufficiency. There are insufficient data as to the extent to which plasma leakage and hemoconcentration contribute to this form of shock.

In shock precipitated primarily by loss of arteriolar vasomotor function -i.e., low peripheral resistance—the first line of circulatory defense remains intact. Therapeutic considerations are primarily mechanical, aimed principally at preventing arterial blood pressure from falling to a level inadequate to sustain adequate blood flow to vital organs. Although adequate tissue blood flow can be maintained at hypotensive levels in the presence of lowered peripheral resistance, as arterial blood pressure approaches zero, tissue blood flow may decrease sharply, presumably from passive collapse of the vascular walls and from increased blood viscosity as a result of impaired "streamlining" of blood flow.87 If such critical arterial blood pressure levels are not reached and tissue blood flow is not acutely curtailed, hypotension resulting from lowered peripheral resistance may be tolerated without an irreparable state's developing. Either the animal dies as the direct result of an inadequate blood flow to the vital centers, or recovery ensues when peripheral resistance is elevated.3 Cardiac failure is not generally evident, since the reduction in coronary blood flow during systemic arterial hypotension is usually proportionately less than the resulting decrease in cardiac work. 88, 89 With coronary atherosclerosis, however, the relation between coronary flow and cardiac work may be reversed.90

## CLINICAL INDICATIONS FOR VASOPRESSOR THERAPY

It would appear that the physiologic mechanism of generalized and persistent peripheral arteriolar constriction which maintains systemic arterial blood pressure and diverts blood to the vital organs during low blood volume shock may, by contrast, contribute, when sustained, to the development of the irreversible phase. Supporting evidence for this premise is available. Following hemorrhage, the activation of sympathetic vasoconstrictor impulses accelerates circulatory failure. 91, 92 During traumatic shock, vaso-

constriction is more intense than following hemorrhage, presumably as a result of reflex response to afferent nervous impulses from the injured areas. Traumatized animals die with residual circulating blood volumes significantly higher than in those subjected to hemorrhagic shock. After section of the dorsal root which abolishes this reflex vasoconstriction, traumatized animals survive until the circulating blood volume has fallen to comparable levels lethal for animals subjected to hemorrhage.93 The generalized arteriolar constriction consequent to low blood volume shock thus seems to exert two major actions:

Arteriolar Vasoconstriction during Low Blood Volume Shock

Immediate

Delayed

saving.

Maintains blood flow to organs re- Decreases blood flow to organs unguired for immediate survival. Life- necessary for immediate survival. Accelerates irreversibility.

The rationale of vasopressor therapy during shock can largely be resolved to the issue of arteriolar constriction and alteration in tissue blood flows. If pressor agents act by enhancing the existing heightened peripheral arteriolar vasoconstriction, it would be expected that such agents might be beneficial as early, short-term therapy, and contraindicated for prolonged use. However, vasopressor agents do not exhibit the same activity in the normal as in the shocked animal. With norepinephrine as the example, pressor agents may increase arterial blood pressure during low blood volume shock primarily by increasing cardiac output. 94-96 At least three mechanisms can be implicated: (1) intensification of capillary vasomotion, which during the early phases of low blood volume shock is hyperresponsive to vasopressor agents,25,26 and results in reduced filling of the capillary bed, increased resorption of interstitial fluid, increased venous return, and an increased, effective circulating blood volume; effective circulating blood volume in the dog can be augmented 20% by norepinephrine; 97 (2) enhancement of coronary blood flow, 98, 99 which may result in improved myocardial function; (3) direct stimulation of myocardial contractility. 100-104 The order of importance of these factors for the increased cardiac output during vasopressor therapy is uncertain. During the later stages of hemorrhagic shock, pressor agents may fail to increase cardiac output significantly; 94,98 nevertheless, they may permit maintenance of cardiac output at levels above those of untreated animals. 105

In the experimental animal, it would therefore appear that norepinephrine should be of value as adjuvant therapy during low blood volume shock, or at least should not be detrimental. Experimental studies bear this out. Vasopressor agents have been reported to decrease mortality in dogs and rats subjected to hemorrhagic shock, even when employed in the late stages; 105-107 although other studies in dogs failed to demonstrate any beneficial effects, 98, 99, 108, 109 no study has indicated an adverse effect unless large doses inducing cardiac arrhythmias were given. The effect of vasopressor agents on cardiac output and survival rates in shock syndromes precipitated by conditions which directly impair capillary vasomotion has not been studied sufficiently; increases in cardiac output probably would be deficient because of the impaired responsiveness of the minute vascular bed.

The effect of vasopressor agents on the mammalian peripheral vascular system is not uniform. Not only do the peripheral vascular effects differ in the normal and shocked animal, but species differences also occur. 95 Although cerebral blood flow is increased during vasopressor therapy in humans made acutely hypotensive with ganglionic blocking agents, 110 and the initial clinical improvement often attendant upon the administration of vasopressor agents during various shock states strongly suggests that such therapy improves blood flow to the vital organs, the effect of vasopressor drugs on cardiac output and individual tissue blood flows during various shock states in man has not been adequately evaluated. There is no suggestion as to the effect on mesenteric blood flow, a factor which appears to be vitally concerned with the development of irreversible low blood volume shock, at least in the experimental animal. Until sufficient evidence is collected by controlled clinical studies proving that the routine use of vasopressor agents during human shock is not detrimental, it would appear prudent to limit vasopressor therapy to selected clinical situations. These might be considered as follows:

1. Peripheral circulatory failure secondary to loss of arteriolar vasomotor function. This is the sole shock syndrome in which vasopressor therapy, by increasing arteriolar tone, may correct specifically the underlying physio-

logic derangement.

2. Central circulatory failure secondary to coronary thrombosis. Coronary artery blood flow is sustained by adequate diastolic arterial blood pressure. As indicated, vasopressor agents increase coronary blood flow during experimental hypotension; oxygen tension of ischemic myocardial tissue has been shown to be increased by norepinephrine. Moreover, vasopressor agents exert a beneficial effect by directly increasing myocardial contractility without disproportionately increasing the requirement for coronary blood flow. Vasopressor agents should therefore be useful after myocardial infarction associated with hypotension and impaired filling of a partially thrombosed coronary artery or sclerotic coronary collaterals. Confirmation of the efficacy of such therapy is found in controlled studies of patients with shock following myocardial infarction. Associated with shock following myocardial infarction.

3. Peripheral circulatory failure associated with suspected coronary or cerebral atherosclerosis. Vasopressor therapy is indicated to elevate arterial blood pressure and thereby sustain coronary and cerebral blood flow until

definitive measures for improvement of the peripheral circulatory failure can be instituted. The effect of arterial hypotension on the clinical aspects of cerebral insufficiency has recently been documented.<sup>116</sup>

4. Extreme depression of systemic arterial blood pressure associated with clinical signs of inadequate coronary or cerebral blood flow. Although marked peripheral vasoconstriction is usually evident during the shock syndrome, serving to enhance blood flow to the vital organs, the increased cardiac output resulting from use of vasopressor agents may further increase blood flow to these organs. Vasopressor drugs, however, are intended as an immediate, lifesaving stopgap procedure until definitive measures are instituted. Nevertheless, if definitive therapy such as fluid replacement fails to correct the shock state, the continued administration of vasopressor therapy seems justified. In the dog and the rat, decreased mortality may result if norepinephrine is administered continuously during the "irreversible" stage of hemorrhagic shock following blood replacement. There are also clinical impressions that the continuous infusion of norepinephrine decreases mortality in human surgical shock despite refractoriness to fluid replacement.

Whether any one of the various vasopressor drugs available commercially is more efficacious than the others in the treatment of shock is a moot question. Angiotonin is not available for routine clinical use. This substance is unique among vasopressor agents in raising *normal* mammalian systemic arterial blood pressure without reducing capillary blood flow in "nonvital" tissues. Angiotonin will elevate arterial blood pressure during the early phases of hemorrhagic shock, but the mechanisms of action have yet to be evaluated.

# Appraisal of Recent Studies on Vasopressor Therapy in Shock of Infectious Origin

Weil <sup>5</sup> reported that, of 15 patients treated with a vasopressor agent (Aramine) for shock subsequent to infectious disease and septicemia, 10 (66.6%) eventually succumbed. There are no data, however, for comparable groups of patients treated without pressor drugs, hence conclusions with respect to the value of such treatment remain speculative. Norepinephrine has been employed during the shock phase of epidemic hemorrhagic fever; the continuous intravenous infusion usually raised arterial blood pressure but failed to alter significantly the impaired peripheral capillary vasomotor activity <sup>81</sup> or the mortality. <sup>128</sup>

In one study of bacterial endotoxin-induced shock, venous return in dogs was measured with and without vasopressor therapy. 124 It was concluded that as a result of therapy, "venous return was effectively increased and the mechanism through which the shock was initiated was therefore counteracted." The studies were limited to the hemodynamic alterations during the initial 30 minutes. The demonstration that vasopressor agents increase

venous return early in the course of endotoxin shock differs in no way from the response during the early stages of most shock disorders; the results provide no clues as to whether pressor therapy actually *counteracts* the mechanism of endotoxin shock or merely *masks* the early manifestations by acting on portions of the vascular system not concerned directly with the immediate fall in arterial blood pressure in the dog. Survival data of vasopressor-treated endotoxin-shocked animals would be of interest, since at least one pressor agent, epinephrine, increases the susceptibility of the host to endotoxin.<sup>126</sup>

## POTENTIATION OF VASOPRESSOR AGENTS BY ADRENAL CORTICOIDS

Although adrenal corticoids may enhance arterial blood pressure responsiveness to vasopressor drugs in normotensive humans, <sup>126</sup> there is no conclusive evidence that adrenal cortical secretion is impaired during most shock syndromes, <sup>127</sup> or that adrenal corticoids administered therapeutically correct the altered arteriolar or capillary vasomotor function or reduce the mortality rate from experimental hemorrhagic or traumatic shock. <sup>128–132</sup> Recent studies indicate that the addition of hydrocortisone to norepinephrine for the treatment of hemorrhagic shock in the rat confers no beneficial effects on survival beyond that of norepinephrine alone. <sup>106</sup> While corticoids have at times potentiated inadequate pressor responses to norepinephrine during cardiogenic and low blood volume shock in the human, in our experience survival has not been enhanced appreciably at this stage.

## EFFICACY OF ANTIPRESSOR AGENTS IN SHOCK

Since prolonged arteriolar constriction contributes to the irreversibility of low blood volume and perhaps of cardiogenic shock, it is conceivable that ganglionic or adrenergic blocking agents should be beneficial; and, indeed, the inhibition of arteriolar constriction by sympathectomy or by ganglionic or adrenergic blocking agents administered prior to the onset of experimental hemorrhagic or traumatic shock does reduce significantly the appearance of the irreversible phase and the mortality rate. 188-145

The effectiveness of adrenergic blocking agents in experimental hemorrhagic shock is in part related to the methods employed by the investigator. Thus, with rapid large bleedings, animals with sympathetic inhibition succumb more readily than do normal animals. However, in the more frequent experiments wherein animals are bled solely to attain a certain standardized lowering of arterial blood pressure, less bleeding is necessary for those animals prepared with the blocking agents than for the control group; i.e., the blocking agents permit a small blood loss to lower arterial blood pressure sufficiently to simulate the effect of a larger bleeding. Although the hypotension achieved is comparable, animals pretreated with the adrenergic blocking agents have a greater residual blood volume, and this, coupled

with the lowered peripheral resistance, undoubtedly permits more effective peripheral tissue blood flow. The efficacy of the adrenergic blocking agents, however, cannot be attributed entirely to such a mechanism, since pretreated animals may be protected against traumatic shock as well as against shock produced by graded hemorrhage despite equivalent blood loss lethal to untreated animals. 138-135, 139, 141, 145, 146 Indeed, certain adrenergic blocking agents that have been modified so that the blocking effect is inhibited (G-D 131)\* may still provide significant protection against development of irreversibility of hemorrhagic shock.147 Moreover, pretreatment with G-D 131 (or with unmodified adrenergic blocking agents) of rats subjected to temporary occlusion of the superior mesenteric artery significantly reduces the 48-hour mortality rate. Although the precise mechanism of therapeutic benefit is unknown, the resultant reduction of the vascular congestion and pooling in the jejuno-ileal region following the localized intestinal ischemia have been postulated as probable important factors. 148 Adrenergic blocking agents may be efficacious if administered early in relatively small dosages after experimental low blood volume shock has been initiated, 137 but generally they have been required prior to shock initiation for beneficial effects to be produced consistently. At present there appears to be no rationale for the clinical employment of adrenergic blocking agents in patients presenting with the shock syndrome. Indeed, it would be hazardous to administer adrenergic blocking agents when hypotensive arterial blood pressure levels already exist despite intense peripheral vasoconstriction. However, the prophylactic employment of adrenergic blocking agents for humans facing exposure to supervised low blood volume shock (extensive surgical procedures) appears to warrant intensive clinical trial. The therapeutic possibilities of combined employment of ganglionic blocking agents (to reduce peripheral arteriolar vasoconstriction) and vasopressor agents (to increase cardiac output) during low blood volume shock also have yet to be explored.

## SUMMARY

The ability of the normal animal to maintain an adequate systemic arterial blood pressure despite a blood volume considerably smaller than the capacity of the vascular bed depends in part upon physiologic control by peripheral vasomotion. This vasomotor process is essentially a dual system. Capillary vasomotor activity comprises the first line of defense, and arteriolar vasomotion represents the second line of defense, preventing blood from entering, distending and pooling within the capillary reservoir. During the early phase of low blood volume shock, both the capillary apparatus and the arteriolar vasomotor apparatus exhibit an intensification of constrictor activity. At this stage the capillary system is highly responsive to vasopressor agents. As shock progresses the capillary vasomotor process, at

<sup>\*</sup> N-(2-chlorethyl)-N-(cyclohexylmethyl)-ethylamine HCl.

least in the mesenteric area, undergoes progressive impairment and becomes increasingly refractory to vasopressor agents, whereas arteriolar constriction is maintained by neurogenic control enhanced by humoral factor activity. The fundamental derangement underlying this impairment of capillary vasomotion appears to reside in tissue ischemia. Sustained arteriolar constriction is an important contributing factor. Although arteriolar constriction serves as an immediate lifesaving mechanism during rapid and severe blood loss, the resultant ischemia in certain tissues (of which the intestine seems to be especially important) hastens the impairment of capillary vasomotor function and the progression to irreversible shock. Hypoxia, release of products of anaerobic tissue metabolism and absorption of bacterial endotoxins probably contribute significantly. The mechanisms of action of vasopressor and antipressor agents during experimental shock have been reviewed. Until data from controlled studies are obtained on the action of vasopressor agents during human shock, it is suggested that vasopressor therapy be reserved for specific clinical situations. These have been considered as selected problems.

### SUMMARIO IN INTERLINGUA

Como consequentia del insufficiente numero de controlate studios clinic, le utilitate therapeutic de agentes vasopressori in varie syndromes de choc human remane controverse. Le presente articulo considera certe conceptos physiologic de choc experimental in relation al application de therapia vasopressori in humanos. Es sublineate le facto que le capacitate de animales normal de mantener un adequate tension de sanguine arterial in le circulation systemic in despecto del presentia de un volumine de sanguine considerabilemente inferior al capacitate del vasculatura depende in parte del regulation physiologic per vasomotion peripheric. Iste processo vasomotori es essentialmente un systema dual. Activitate vasomotori in le capillares es le prime linea de defensa e vasomotion arteriolar es le secunde linea de defensa contra le effortio del sanguine de entrar in le reservoir capillar, de distender lo, e de accumular se in illo. Durante le prime phases de choc per reduction del volumine de sanguine, tanto le apparato capillar como etiam le apparato vasomotori arteriolar exhibi un intensification de lor activitate constrictori. A iste stadio le systema capillar es multo responsive al effecto de agentes vasopressori. Durante que le choc progrede, le processo vasomotori capillar-al minus in le area mesenteric-suffre un progressive deterioration e deveni de plus in plus refractori al effecto del agentes vasopressori, durante que le constriction arteriolar es mantenite per un regulation neurogene que es promovite per le activitate de factor humoral. Le disturbation fundamental responsabile pro iste deterioration del vasomotion capillar pare trovar se in ischemia de histo. Le sustenite constriction arteriolar es un importante factor contributori. Ben que le constriction arteriolar servi como mechanismo de salva-vita immediate in caso de rapide e sever perdita de sanguine, le resultante ischemia in altere histos (inter le quales le intestino pare esser specialmente importante) accelera le deterioration del function vasomotori capillar e le progresso verso choc de forma irreversibile. Hypoxia, le liberation de productos del histometabolismo anaerobie, e le absorption de endotoxinas bacterial es probabilemente factores contributori significative. Es presentate un revista del mechanismo de action de agentes vasopressori e antipressori in choc experimental. Usque datos es obtenite ab studios controlate in re le action de agentes vasopressori in choc human, il es recommendate que therapia vasopressori

es utilisate solmente in le sequente situationes clinic: Disfallimento circulatori peripheric que es secundari al perdita del function vasomotori arteriolar, disfallimento circulatori central que es secundari a thrombosis de arteria coronari, disfallimento circulatori peripheric que es associate con le suspicion de atherosclerosis coronari o cerebral, e extreme depression del tension de sanguine arterial in le circulation systemic que es associate con signos clinic de un inadequate fluxo de sanguine coronari o cerebral.

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## HEREDITY IN ANKYLOSING SPONDYLITIS\*

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As far as is known, the first workers to indicate a hereditary influence in ankylosing spondylitis were the members of the Clinical Club in 1888. Both Sir Jonathan Hutchinson and Alexander Morrison stressed the significance of a family history of rheumatism or gout. Later the adjective "heredo-traumatique" was applied to von Bechterew's syndrome, and Marie and Astié in 1897 1 reported a sister and father who had had a similar disease. Geilinger in 1918 thought that heredity played a part in approximately 10% of cases, but interest in this aspect of the disease waned, apart from sporadic reports of involvement of close relatives. In 1942 Scott 3 described a series of 300 cases among whom were affected combinations of all the close sibships. He and many others described cases of twins having the disease.

In 1948 and 1949 Rogoff and Freyberg 4a, b investigated 114 cases of ankylosing spondylitis and found 30 with suggestive family histories. They examined 24 of these families personally and confirmed ankylosing spon-

dylitis in 13 of them.

A most valuable paper was written by West 5 in 1949. In a careful report on the disease in Bristol he describes having examined personally the families of 85 patients and having found among them 10 further cases of ankylosing spondylitis. This, he thought, indicated a rate 100 times more than the incidence among the general population. In 1955 Stecher et al.6 came to the conclusion that the disease was transmitted by an autosomal dominant factor, with an approximate penetrance of 70% in males and 10% in females.

Many writers—for example, Potter, Stephens and Nunemaker and others on the Continent-have estimated that the incidence of ankylosing spondylitis among the patient's immediate relatives is approximately 10%.

The following observations are taken from a study of the relatives of 87 patients with established disease treated at Charing Cross Hospital.

In this series the hereditary and familial incidence has been investigated under difficult circumstances. Some of the patients had migrated to London from the provinces and had not maintained contact with the rest of their families. Even where the family was still in London it was not found possible to examine all of the relatives personally. A few had no knowledge of relatives (two came from orphanages, and two did not remember or know their parents or family). And finally, several families refused to cooperate.

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TABLE 1
Close Relatives of the Cases of the Series

Primary Cases	Parents	Brothers	Sisters	Total
70	134	184	110	428

A total of 70 families were available for investigation; of these, there were 134 parents, 184 brothers and 110 sisters, excluding the primary cases. (Only the parents and brothers and sisters were investigated.)

The investigation took the form of a detailed questionnaire to each patient regarding the incidence of disease of the back or hands (ankylosing spondylitis \* or rheumatoid arthritis) in his family. The patient was then questioned closely about the members of his or her family, and arrangements were made for individual examination at Charing Cross Hospital or x-ray examination at another hospital, or information about the diagnosis was requested from the respective hospital.

There were 34 positive answers. These were filtered down to 16 certain or very probable cases of familial ankylosing spondylitis and six of rheumatoid arthritis. The methods of confirmation of their diagnosis varied according to the availability of the patient. These were:

- A. Proved by my personal examination.
- B. Proved by examination of x-ray plates from another hospital.
- C. Proved by positive information from another hospital.
- D. Probably proved, by very typical description given of the relative's symptoms by the patient.

While the diagnosis in group D is open to question, every effort was made to achieve certainty, and particular attention was paid to the reported degree of disability of the back or deformity of the hands and age at onset of symptoms, etc., and wherever there was difficulty in distinguishing the description from such conditions as osteoarthritis, spondylosis, or neurologic, gynecologic and congenital lesions, these cases were excluded. The number found is less than the true total because only well established cases were accepted in group 4.

## ANKYLOSING SPONDYLITIS

The number of close relatives affected by the disease appears to be definitely raised above the level in the general population (table 2).

The latter has been estimated by West 5 to be one per 2,000 of the population, using the City of Bristol as a testing place. In this series, among the 428 close relatives of 70 primary cases, there were 16 cases of ankylosing spondylitis, 14 males and two females—that is, one per 28 of close relatives

<sup>\*</sup> In this paper, ankylosing spondylitis and rheumatoid arthritis are regarded as different entities.

was affected. The occurrence of cases in close relatives is far more common than would be expected in the general population, and there can be little doubt that heredity is a factor in the onset of the disease.

The transmission is not through a sex-linked recessive, as might be suggested by the preponderance of males. It will be seen in table 2 that there were six instances where the disease was transmitted from father to son. In human sex linkage the gene is carried on the X-chromosome, and is most commonly transmitted by the female to half of her male offspring. A sex-linked gene cannot normally pass from the father to the son. In ankylosing spondylitis the offending gene obviously does.

TABLE 2
Patients with Close Relatives Suffering from Ankylosing Spondylitis

Case	Sex	Brothers and Sisters		Parents	Close Relatives	Method of
		В	S	Known	with Ankylosing Spondylitis	Confirmation
L. Fr.	M	2B	-	2	1 Brother	В
G. Da.	M		1S	1	1 Brother	C
N. Da.	M	1B	_	2	1 Father	C
W. Br.	M	_	35	2	1 Father	D
C. Ma.	M	1B	15	2	1 Father	C
R. Ri.	M	-	4	2	1 Father	D
W. Be.	M	-	1214000	2	1 Father	D
C. Up.	M	2B	18	2	1 Sister	В
S. Gr.	M	- mine	1S	2	1 Mother	C
A. Sm.	M	2B	28	2	1 Brother	D
S. Jo.	M	1B	3S	2	1 Father 1 Brother	D B C D C
H. Po.	M	_	18	2	1 Brother	D
C. Ja.	M	_	-	2	1 Brother	C
F. Du.	F	2B		2	2 Brothers	B.B.
Totals 14		- 11B	13S	27	8 Brothers 6 Fathers 1 Sister 1 Mother	4B 7C 5D

It is unlikely that the gene is a simple autosomal recessive. This would imply that most cases of ankylosing spondylitis arise from cousin marriages. There was no evidence of consanguinity in this series.

If the genetic factor is neither sex-linked nor recessive, then it may be a simple dominant with differing penetrance for males and females. If one assumes ankylosing spondylitis to be an extreme form of rheumatoid arthritis, and if one adds together the cases of the two diseases, there is a ratio of 14 males to eight females. This is not a significant deviation from equality. The family tree shown in figure 1 suggests that, within a given family, the same genetic factor which in the male produces ankylosing spondylitis in the female produces rheumatoid arthritis. The threshold for ankylosing spondylitis may be higher in females (as is the case with gout), and this may be modified by some factor to allow for an increased likelihood

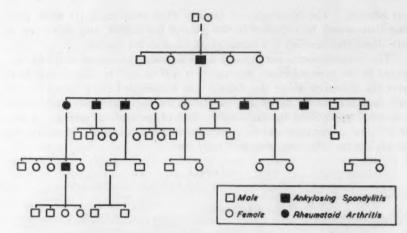


Fig. 1. Diagram representing the family tree of D. Ta. (table 4).

of the disease in families with an affected female. The figures above would support the findings of Hersh, Stecher et al., i.e., that there is a simple dominant with differing penetrance for males and females. For instance, when the gene comes through the father, he has the clinical condition; when it comes through the mother, she rarely has the clinical condition.

# INCIDENCE AMONG CLOSE RELATIVES OF FEMALE CASES

In 1950 Hersh et al.<sup>9</sup> laid emphasis on the increased likelihood of complete penetrance of the heredity factor in families with an affected female. In my series the families with an affected female were not great in number,

Table 3
Incidence of Ankylosing Spondylitis Among Families of Affected Females

Case	Brothers and Sisters		Parents	Close Relatives with Ankylosing	Method of
	В	S	Known	Spondylitis	Confirmation
B. Lo.		15	2 2		-
E. Sp.	4B	2S 3S	2		
H. Re.	1B	3S	2		
R. Br.	_		2		-
L. Ca.	-	15	2		_
W. Hl.	-	25	2	-	- CONTINUE -
F. Du.	2B	-	2	2 Brothers	B.B.
*D. Up.	3B	-	2	1 Brother	A
*B. Gr.	1 Son		-	1 Son	A
Totals 9	10B 1 Son	98	.16 .	3 Brothers 1 Son	2B 2A

<sup>\*</sup> Sister and Mother of C. Up. and S. Gr., respectively, in table 2.

TABLE 4

Number of Cases with Rheumatoid Arthritis among Families with Ankylosing Spondylitis

Case Sex Brothers and Sister	Care	Brothers and Sisters		Parents	Close Relatives	Method of
	S	Known	Arthritis	Confirmation		
P. Bu.	M	_	_	2	Mother	D
E. Va.	M	2B	-	2	Mother	C
D. Ke.	F			1 1	Mother	A
A. Sm.	M	2B	28	2	Sister	D
C. Ja.	M	-	_	2	Mother	C
D. Ta.	M	-		2	Mother	A
Totals 6		4B	25	11 Parents	5 Mothers 1 Sister	2A 2C 2D

or in number of close relatives. Table 3 shows the families of seven female primary cases and two secondary cases. Among 36 close relatives there were four cases of ankylosing spondylitis—that is, one per nine, instead of one per 28, as in the whole series. Certainly the penetrance seems to be increased, the more so if we exclude the female relatives—four males among 19 at risk.

# Association of Rheumatoid Arthritis with Ankylosing Spondylitis

In table 4 I have set out the incidence of rheumatoid arthritis among close relatives of patients with ankylosing spondylitis.

There were six cases, five mothers and one sister—that is, among 428 close relatives of 70 cases of ankylosing spondylitis, one finds six cases of rheumatoid arthritis. This number—one per 71 of all close relatives, or one per 29 of the female close relatives—is greater than one would estimate to be the normal occurrence. By a dubious deduction from the figures of Boland and West, one may assess the incidence of rheumatoid arthritis in the general population as about one per 125. The General Register Office, in a sample study of 10 general practices in 1952–1953, found the incidence to be 4.6 persons per 100 (6.8 females, 1.9 males), or one per 217 of the general population and about one per 70 of the female population. There is in this series an increased frequency between two and three times what one would normally expect, but the numbers are not sufficiently great to be statistically significant.

In the family tree shown in figure 1 this association of rheumatoid arthritis with ankylosing spondylitis appears to be present when ankylosing spondylitis is passed through a mother with rheumatoid arthritis to one of her sons. (The son is D. Ta. of table 4). This pedigree would suggest a common genetic factor.

## Conclusions

1. From this series of cases there is definite supporting evidence for the thesis that there is a strong hereditary factor in the genesis of ankylosing spondylitis.

2. In families where a female is involved there is probably an increased

likelihood that other members will contract this disease.

3. There appears to be an association in this hereditary factor between ankylosing spondylitis and rheumatoid arthritis.

# SUMMARY

From a series of 70 families, evidence is drawn to support the theory that there is a strong hereditary factor in the disease (probably a simple dominant with varying sex penetrance), that it is associated with rheumatoid arthritis in this hereditary aspect, and that when a female contracts the disease there is likelihood that other members of her family will be affected.

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#### SUMMARIO IN INTERLINGUA

Le prime investigatores qui indicava un influentia hereditari in spondylitis ankylosante esseva le membros del Club Clinic in 1888 (Sir Jonathan Hutchinson e Alexander Morrison). In 1897, Marie e Astié describeva un occurrentia familial. In 1918, Geilinger opinava que le hereditate ha un rolo in 10% del casos. In 1942, in un serie de 300 casos, Scott trovava numerose familias con plure membros afficite.

Rogoff e Freyberg investigava le question in 1948 e 1949. West faceva le mesmo in 1949 e Stecher et al. in 1955. Omnes trovava un distincte relation. In 1950, Potter se trovava de accordo con lor conclusiones. Le mesmo vale pro Stephens e

Nunemaker, qui reportava lor constatationes etiam in 1950.

In le presente studio, le consanguineos de 70 patientes esseva examinate, incluse un total de 428 fraternos. Spondylitis ankylosante e arthritis rheumatoide esseva

tractate como duo differente entitates.

Le investigation resultava in le discoperta de 16 casos secundari de spondylitis ankylosante e sex casos de arthritis rheumatoide. Nulle evidentia supportava le these de un recessive gen a specificitate sexual como vehiculo del transmission. Le mesmo valeva pro le supposition de un simple recessive gen autosomal. Es exprimite le opinion que le factor esseva un dominante simple con differente grados de penetrantia in masculos e in femininas.

In 1950, Hersh et al. reportava un augmentate probabilitate de penetrantia complete del factor hereditari in familias in que un feminina es afficite. Certe observa-

tiones in le presente serie supporta ille these.

Un association inter spondylitis ankylosante e arthritis rheumatoide esseva incontrate con un frequentia de duo a tres vices illo characteristic del population general, sed le numeros in le investigation non sufficeva pro permitter un conclusion firme. Un arbore genealogic es includite in supporto del these de un commun factor genetic. In le familia in question, spondylitis ankylosante esseva transferite ab un granpatre a un granfilio via un matre qui habeva arthritis rheumatoide.

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# CHEMOTHERAPY OF MALIGNANT TUMORS\*

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A DEVELOPMENT of the problem of the drug therapy of cancer is possible along two main roads. The first is the development of methods for the medicinal stimulation of the protective forces of the organism in relation to the developing tumor, for the purpose of obtaining a regression of the process or, at least, the cessation of its further spread. The second is the search for medicinal preparations which can bring about the death of the tumor by means of direct interference with the metabolism of the malignant tissue (chemotherapy proper).

A review of the first steps along the road of the drug therapy of cancer will not be the crux of the present paper. For purposes of organization, let us recall only that these consisted of attempts to influence the course of cancer by means of stimulation of the connective tissue system (injection of ATsS; A. A. Bogomolets and his school) and activation of the processes of immunity (injection of vaccines and immune sera). Despite the numerous attempts, they did not lead to the development of clinically justifiable methods.

The factual data and theoretic considerations at hand give us the well known bases for stating that even a successful realization of a stimulation of the protective forces of the body and the processes of immunity against tumors could hardly be a leading method in the treatment of cancer, especially of primary tumors. However, the development and use of the methods in question as auxiliary means in the treatment of tumors are quite suitable.

Historically, the first form of chemotherapy in the narrow sense of the word seems to be the use of hormones. This is based on the attempt to neutralize (by means of drugs) the action of the hormonal stimulators of the metabolism in the cancer cells. This is found to be possible because tumors of certain organs retain the ability to respond to these stimulators in the same way as do the original normal cells.

Thus, it is known that the metabolism, growth and cell multiplication of the prostate gland are stimulated by the male sex hormone. In cases of discontinued production of the latter (for example, after castration), the

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gland atrophies. The same thing takes place with tumors of the prostate gland. This effect can also be attained by means of an injection of the female hormone or its substitutes (sinestrol and others), thanks to which a type of chemical castration or, possibly, neutralization of the action of the male hormone, takes place.

Application of this method in cancer of the prostate gland showed that a significant, immediate therapeutic effect is often observed, even in the faradvanced stage of the disease—for example, in the presence of metastases to the bones. The At the same time it was found, first, that not all forms of cancer of the prostate gland yield to this treatment, and, second, that the tumor tissue does not disappear completely but only undergoes atrophy and metaplasia. For these reasons, renewed tumor growth takes place upon discontinuation or even during interruptions of the treatment. Besides, resistance of the tumor cells to further application of the preparations is gradually developed. All this leads to the conclusion that, in the majority of cases, the treatment will have an effect for no longer than two years.

Approximately the same principles and the same results also hold true for the use of the male sex hormone (testosterone) in cancer of the breast in relatively young women, sometimes in the presence of metastases to the bones. We will therefore not go into this further. Let us note only that in older women (after the onset of menopause) a positive therapeutic effect is obtained not only from testosterone but also from substances with female hormone activity. However, we are probably also dealing here with elimination of stimuli for the growth of the cells of the breast, except that these stimuli are elaborated not by the ovary but by the hypophysis. Apparently the gonadotropic hormones, the production of which is inhibited by large doses of estrogens, can be such stimuli.

If in hormonal therapy we make use of the similarity between the properties (and the reactions) of malignant and normal tissues, then all the remaining methods of chemotherapy and the directions of research into anticancer preparations are based on the essential differences between them. Unfortunately, the qualitative biochemical characteristics of tumor tissues have been insufficiently studied. Therefore, the investigation and use of the antitumor preparations have so far been based more on the quantitative differences and only partially on the scanty information concerning the characteristics of the enzymes and metabolism of malignant and normal tissues. To this class belongs, apparently, for example, the use of the phosphate ether of diethylstilbestrol (the preparation Khonvan). The latter is biologically inactive and has almost no estrogen activity. Nevertheless, its clinical use in cancer of the prostate gland gives even better results than does diethylstilbestrol itself.278 The suggestion is made that in tumors of the prostate gland, which are richer in acid phosphatase than is the normal tissue, Khonvan undergoes dephosphorylation, resulting in the formation of free diethylstilbestrol, which then exerts its activity.

The suggestion that the  $\beta$ -glucuronide of the nitrile of mandelic acid (the preparation Letril)<sup>31</sup> be used as an anticancer preparation is based on the richness of some tumors in  $\beta$ -glucuronidase, under the influence of which the cyanogenic glucuronides liberate hydrocyanic acid. There are also data indicating that normal tissues are relatively rich in the enzyme which transforms cyanates into the weakly toxic rhodanates. At the same time, tumors contain very little rhodanase and are therefore unable to detoxify hydrocyanic acid. According to the preliminary data, clinical trials of Letril (local application to various superficial cancers) have given favorable results.

The antimetabolic direction in chemotherapy is based on the attempt to inhibit the quantitatively increased synthesis of nucleic acids and proteins in malignant tumors with the aid of metabolic antagonists. Attempts at inhibiting nucleic acid synthesis in tumors with the aid of purine and pyrimidine derivatives as possible antimetabolites of nucleic acid metabolism were begun by us together with N. V. Lazarevyi in 1946. It was found that a series of pyrimidine derivatives actively inhibit the growth of various transplanted tumors.<sup>8b</sup>

In 1948 Farber <sup>28</sup> and others attempted to affect malignant processes by the use of folic acid antagonists (aminopterin and others) which, because of competition with folic acid, hinder the formation of the purine bases. Aminopterin has a therapeutic effect in the acute leukoses (hemocytoblastoses) of children, producing a remission of a few weeks or months (up to two years). The recurrences yield to the treatment less well and, finally, drug resistance is developed due to adaptive changes in the metabolism of the leukemic cells.

It was later found that certain purine derivatives, e.g., 8-azaguanine and 6-mercaptopurine, also hinder the synthesis of nucleic acids and have an inhibitory effect on the growth of certain animal tumors. Mercaptopurine has found clinical application in acute leukoses, in which it has approximately the same effect as aminopterin.

Attempts have been made to inhibit the rapid synthesis of proteins in tumors with the aid of amino acid derivatives. Thus, we discovered the inhibitory effect of specially synthesized derivatives of lysine (benzoyl lysine and others) on the growth of various tumors. Levi and co-workers studied the effect of a methionine homologue, ethionine. However, the use of antimetabolites of protein metabolism for the treatment of tumors has not so far gone beyond the experimental stage. Despite the to date modest practical results, the idea of treating tumors with the aid of antimetabolites deserves ultimate development. Apparently it is necessary to proceed along the line of acting not on just one, as has most often been done up to the present time, but simultaneously on various forms of metabolism.

The attempt to inhibit the multiplication of tumor cells lies at the basis of those directions in tumor chemotherapy which are inclined to use sub-

Fig. 1. 6-mercaptopurine.

stances of microbial origin and substances from the higher plants (the socalled mitotic poisons) for this purpose.

The search for "antibiotics" against tumors rests on the hypothesis that there are general mechanisms for the inhibition of multiplication of both bacteria and tumor cells. The first such preparations were actinomycins (C and D), occurring as a red dye associated with a peptide side chain. In experiments on animals, actinomycin was found to have a weak inhibitory effect on various tumors. However, in clinical trials a therapeutic effect has been noted only in lymphogranulomatosis in the very early stages 48

Another antibiotic was azaserine, produced and studied by a large group of American authors, and consisting of the amino acid so the carrying a diazocetyl group which is very active chemically (alkalizing activity). In experiments on animals an inhibitory effect of azaserine on the growth of various tumors was noted, but only in toxic doses. (No real therapeutic effect was detected on malignant tumors in clinical trials with therapeutic doses. Besides, the preparation was found to have significant side-effects on the gastrointestinal tract, liver and pancreas.)

General interest has been aroused by the report of Japanese authors to concerning their isolation of an antibiotic called Sarcomycin from the nutrient medium of one of the actinomycetes. Its structure has been determined by a group of American investigators. It was found to be 2-methylene-3-keto-cyclopentanocarbonic acid. In experiments on animals, Sarcomycin was found to have relatively weak antitumor activity in the presence of very little toxicity. Clinical trials of the preparation were carried out on a large number of patients with various malignant tumors in the far advanced stage. According to the author's report, a favorable effect was obtained in individual patients, for example, in metastases of cancer of the stomach to the lymph nodes and in chorio-epithelioma of the lung. However, subsequent authors denied the real therapeutic effect of Sarcomycin. 2

Fig. 3. Sarcomycin.

In joint work of the Institute of Antibiotics of the Ministry of Health of the U.S.S.R. and the Institute of Experimental Pathology and Therapy of Cancer of the Academy of Medical Sciences of the U.S.S.R., the antibiotic Actinoxanthin was recently found to have antitumor activity which could be demonstrated on animals.<sup>14</sup> No clinical trials have yet been carried out with this compound.

Thus, the search for anticancer preparations among the "antibiotics" has not yet led to any real practical successes.

As to substances of microbial origin, one should not forget the polysaccharides isolated from *Bacterium prodigiosum*.<sup>42</sup> These substances produce hemorrhage and necrosis in animal tumors, reminding one of Shwartzman's phenomenon. Careful studies have shown, however, that, notwithstanding widespread necrosis, viable cells are completely preserved in the peripheral portions of the tumors, thus making possible renewed growth. The abovementioned polysaccharides, which produce significant toxic manifestations, have not found clinical application.

Among the substances of plant origin, practical significance has been acquired by podophyllin and two alkaloids from *Colchicum autumnale*, colchicine and colchamine (omaine). Colchicine has been known for a long time as a mitotic poison, but its significant toxicity interfered with its clinical application, although it was found that disintegration of the tumor tissue took place after its local action on skin cancers.

In 1950, in the VNIKhFI (All-Union Chemo-Pharmaceutical Scientific Research Institute),6 and almost simultaneously and independently abroad, from the same plant, another alkaloid was isolated, called colchamine or omaine, and differing from colchicine in the absence of the CO group in the side chain on ring B. During an experimental study of this compound by E. M. Vermel, it was found that it is less toxic and that its action on tumors is more pronounced. Omaine first found clinical application in the form of an ointment (0.5%) for the local treatment of skin cancer. According to present data, 3a, 15 the omaine treatment produces a cure in 95% of the patients with the early stages of skin cancer. During this treatment the tumor tissue disintegrates and tears away so that an ulcer is formed initially, which then achieves granulation and leaves a delicate scar. Although the early stages of skin cancer can be cured surgically and by radiation, the treatment with omaine has attracted great interest, principally because of the significant selectivity of its action. Omaine rapidly brings about the lysis of tumor cells while exerting only a weak effect on the surrounding normal tissues.

It was later shown that omaine has a therapeutic effect on myeloid leukemia when given internally.<sup>41</sup> Upon further use of both omaine itself and preparations which are close to it (desacetylthiocolchicine), it was found that they also have a therapeutic effect on other tumors when given intravenously, for example, in cancer of the esophagus,<sup>36</sup> which points to the possibility of widening its sphere of application.

The greatest practical results have been attained in the use of the so-called alkylating compounds for tumor chemotherapy. The first such compounds were the  $\beta$ -chloroethylamines of the aliphatic series, namely, the hydrochlorides of methyl-di(2-chloroethyl)amine and tri(2-chloroethyl)amine, which are still characterized as nitrogen analogues of yperite (or simply as nitrogen mustards), according to which they differ from yperite by the fact that the sulfur atom in these compounds is replaced by nitrogen.

They were suggested as medicinal preparations in 1946 by a group of American authors 30, 80 for the treatment of chronic leukoses and lymphogranulomatosis. In the U.S.S.R., the first of these compounds received the name Embikhin. Later (1951), as the result of our experimental work, another preparation was selected, namely 2-chloropropyl-di(2-chloroethyl)-amine, which received the name Novoembikhin. The latter has the advantage that its side-effects on the gastrointestinal tract and its depressive effect on blood formation in the bone marrow are less pronounced.

Japanese authors have suggested the use of the N-oxide of Embikhin (the preparation Nitromin), which is distinguished by a lower toxicity.40

Fig. 5. Novoembikhin.

It is claimed that the chloroethylamines of the aliphatic series undergo an intramolecular cyclization in aqueous solutions with the formation of a three-membered ethylenimino ring. The latter is very unstable and is easily ruptured with the freeing of a valence bond at the beta carbon atom, at which site an alkylation reaction readily takes place with various chemical groups in biologic compounds (for example, with amino groups, the hydroxyl group, the carboxyl group, etc.).

In therapeutic doses, the chloroethylamines apparently first react with the

highly active nucleoproteins of the cell nuclei of proliferating tissues, especially the hematopoietic tissues. As a result of the fact that only compounds having at least two chloroethyl groups on the nitrogen appear to be biologically active, it is suggested that they form transverse linkages between parallel chains of the highly polymerized desoxyribonucleic acid.<sup>24</sup> As a result of this, the physicochemical state and the metabolism of this important compound are disrupted and the cells lose their vital capacity, while the increasing activity of the lytic enzymes leads to their lysis.

The above-mentioned preparations are used mainly for the treatment of tumors and closely similar diseases of the hematopoietic system, such as lymphogranulomatosis, myeloleukoses and lympholeukoses and erythremia, i.e., diseases characterized by excessive formation of pathologic tissues rich

in active desoxyribonucleoproteins.

In the chronic myeloleukoses, the chloroethylamines produce remissions, with amelioration or disappearance of the clinical symptoms of the disease and improvement in the condition of the blood and bone marrow so that they become almost normal. This can be achieved even in the far advanced stage of the disease. The remissions last from two to six months, after which a relapse occurs which requires a new course of treatment.21 However, in the majority of cases the treatment does not continue to yield results beyond three years. The favorable effect can be more prolonged in the lympholeukoses.

By treating lymphogranulomatosis with Embikhin and Novoembikhin according to a specially developed method,9 one may obtain not only a good immediate therapeutic effect (complete disappearance of the symptoms of the disease) but also satisfactory remote results. Thus, according to the data of the author, of the patients whose treatment was begun in the relatively early stages of the disease at the Oncological Institute of the Academy of Medical Sciences of the U.S.S.R. during the years 1949-1951, about 50% survived and were able to work for from five to eight years after the beginning of treatment.10 These results are better than those obtained with x-ray treatment of lymphogranulomatosis at the same institute. When the treatment is begun in the moderately and far advanced stages, it is also possible to obtain a good immediate effect in some patients, but the remote results are significantly poorer.

In the majority of true malignant tumors having no relation to the bloodforming tissues, the chloroethylamines of the aliphatic series are ineffective. We have data only on the possibility of obtaining therapeutic results from cancer of the breast and metastases to the lymph nodes,12 and in chorio-

epithelioma, and on the palliative effect in cancer of the lung.

Starting from the assumption that the chloroethylamines undergo intramolecular cyclization in aqueous solutions with the formation of an ethylenimino ring, a series of authors have suggested compounds with preformed ethylenimino rings as therapeutic preparations. 4, 26, 34 These include

Fig. 7. TEP.

triethyleniminotriazin (the preparation TET), triethylenphosphoramide (TEP), triethylenthiophosphoramide (Thio-TEP) and others.

However, these preparations, as well as Myleran (1,4-dimethylsulfo-hydroxybutane), <sup>29, 33</sup> which was suggested almost simultaneously, are also used principally in those same diseases of the hematopoietic system which are treated with the chloroethylamines of the aliphatic series, and they have no effect (or only a weak one) on tumors of other organs.

It was thus necessary to search for ways of strengthening the antitumor effect of the chloroethylamines and ethylenimines and directing their activity at the true tumors. In searching for these ways, we suggested that the chloroethylamino and ethylenimino groups be united with biologically important compounds which play a role in metabolism—for example, the amino acids—as well as with the heterocyclics, which enter into the structure of the nucleic acids, vitamins and coenzymes. It was assumed that these compounds could serve to carry and guide the alkylating groups into the tumors, which seem to be a focal point for the synthesis of protein, nucleic acids and other compounds.

Proceeding from these thoughts, we synthesized the chloroethylamine derivatives of pyridine, pyrimidine, thiazole, benzimidazole and phenylalanine. The majority of these compounds actually exerted a more pronounced antitumor activity than did Embikhin in the laboratory. The best properties were shown by 4-methyl-5-di-(2-chloroethyl)aminouracil, which received the name Dopan, and dl-N-di(2-chloroethyl)-aminophenylalanine, which was called Sarcolysin. 13, 19, 20 \*

Thus, Sarcolysin produces complete resorption of a rat sarcoma 45 weighing a few grams in all animals. It is even possible to obtain resorp-

<sup>\*</sup> This same compound was prepared independently by Bergel and Stock in England.25

tion in such a case if the tumor accounts for 20% of the weight of the body. The strength of the therapeutic effect depends to a great degree upon the method of application.<sup>5</sup> The effect of Sarcolysin and Dopan is aimed directly at the tumor. Thus, by the use of doses of Sarcolysin and Dopan which are just insufficient for complete resorption, strains of sarcoma 45 are obtained which are resistant to these preparations, the resistance being maintained during subsequent transfers.<sup>22</sup> If one inoculates the same animal with the usual strain on the one side and with the resistant strain on the other, and then provides treatment, the resistant tumor continues to grow at the same time that the usual one is being resorbed. This could not take place if the effect of Sarcolysin were exerted in an indirect way. Indirect evidence has also been obtained that Sarcolysin in therapeutic doses is selectively bound to a certain degree by the tissues of sensitive tumors.

The spectrum of the antitumor action of Sarcolysin and Dopan has been found to be quite broad in transplanted tumors, but various tumors have varying sensitivities. Besides, a certain difference in the spectrum of action of the two preparations has also been noted. These data have also been confirmed clinically.

It was found that certain human tumors are very sensitive to Sarcolysin—for example, seminomas (especially their lymphatic metastases), reticulosarcomas and Ewing's bone tumor—and that they disappear under its influence.¹ A therapeutic effect was also noted in multiple myeloma and in primary cancer of the liver proceeding from the bile ducts. Several patients with healed seminomal metastases have already been followed (without recurrences) from one and one-half to two and one-half years.

At the same time, Sarcolysin has no therapeutic effect on many other tumors (for example, osteosarcoma, sarcoma of the soft tissues, lung cancer, and cancer of the stomach). This shows again that it is hardly possible to find a universal antitumor preparation, and that it is necessary to synthesize individual preparations for tumors of various organs and tissues in agreement with the great differences in their metabolism.

The difference in the spectrum of action of Sarcolysin and Dopan, which have the same active chemical group on different "carriers," gives one the right to suggest that it will be possible to obtain new preparations by means of exchanging certain "carriers" for others, e.g., replacing phenylalanine (in Sarcolysin) by other amino acids. In this it should be kept in mind that the utilization of the various amino acids by tumors is quite different.

While searching for new preparations of this type, we investigated the dipeptides of Sarcolysin, i.e., compounds between it and other amino acids.

The synthesis of these compounds has been accomplished by I. L. Knunyants and his co-workers.<sup>7</sup> The first experiments on animals showed that peptides containing N-formylsarcolysin with phenylalanine and valine retained their antitumor activity while completely losing their toxicity (Z. P. Sof-ina). It is possible that these compounds become active in tumor tissues after splitting of the peptide bond and the "liberation" of Sarcolysin.

Fig. 10. N-formylsarcolysylvaline ethyl-ester.

In this way, still another means of synthesizing antitumor preparations has been discovered, involving the addition to Sarcolysin (or to the chloroethylamine derivatives of other amino acids) of a series of biologically active compounds, for example (besides the amino acids), vitamins, hormones, lipids, etc., which are closely connected with the metabolism of various tissues and therefore of various tumors.

### SUMMARIO IN INTERLINGUA

Iste revista se occupa de ille agentes de chimotherapia anticancerose que age per obstruer le metabolismo del cellula concerose plus tosto que per stimular le defensas del corpore contra le crescentia neoplastic. Es discutite le theoria, le modo de action, e le effectos therapeutic del varie gruppos de compositos.

Le therapia hormonal utilisa le similaritate inter le reactiones de histos maligne e le reactiones de histos normal de organos particular al stimulation endocrin e servi como controlo o neutralisator de ille stimulation. Usualmente su effecto therapeutic

non pote esser mantenite durante plus que duo annos.

Per contrasto con le therapia hormonal, le methodologia chimotherapeutic que labora con antimetabolitos es basate super le differentias essential que existe inter cellulas normal e cellulas cancerose. Es mentionate particularmente le resultatos obtenite per medio del antagonistas de purina, pyrimidina, e acido folic. Inter istos, 6-mercaptopurina e aminopterina effectua resultatos benefic in le leucemias acute. Lysina benzoylic, un derivato de lysina, e ethionina, un homologo de methionina, ha essite testate contra tumores experimental. Laetrilo, le glucuronido beta de mandelonitrilo, ha producite effectos favorabile contra tumores superficial.

Substantias de origine microbial e vegetal es usate in le effortio de inhibir le multiplication de cellulas tumorose. Le polysaccharidos ab Bacterium prodigiosum es multo toxic. Colchamina, i.e. deacetyl-N-methylcholchicina, es minus toxic e plus efficace que colchicina. Quando applicate localmente durante le prime phases, illo produce un curation in 95% del patientes con cancere cutanee. Le uso de colchamina e etiam de desacetylthiocolchicina is currentemente extendite al tractamento de can-

cere del esophago.

Le cerca de antibioticos es basate super le theoria que le proliferation de cellulas tumoral e de organismos microbial es sensibile al mesme mechanismos inhibitori. A parte le ben-cognoscite antibioticos, actinoxanthina es mentionate como un agente

que ha monstrate un activitate antitumoral in experimentos animal, sed usque nunc le application de iste gruppo de substantias ha non ancora resultate in successos practic.

Înter le varie classes de compositos studiate, le agentes alkylante ha producite le plus extense beneficios usque al tempore presente. Le beta-chloroethylaminas, le prime tal compositos, reage con le nucleoproteinas del nucleos cellular de histos proliferante, formante—apparentemente—ligationes transverse inter le catenas parallel del altemente polymerisate acido disoxyribonucleic. Lor activitate biologic depende del presentia de al minus duo gruppos chloroethylic attachate al atomo de nitrogeno. Embikhina, i.e. methyl-bis (2-chloroethyl) amina, e su minus toxic analogo novoembikhina produce remissiones de un duration de inter duo e sex menses in patientes con chronic leucemia myeloide. Repetite tractamentos pote resultar in remissiones de usque a tres annos de duration combinate. In le leucemias lymphatic, ancora plus prolongate effectos pote esser producite. Quando applicate in le prime stadios de lymphogranuloma, iste mustardas de nitrogeno ha resultate in superviventias de inter cinque e octo annos in 50% del patientes tractate.

Le observation que chloroethylaminas in solutiones aquose experientia cyclisation intramolecular con le formation de un nucleo ethyleniminic duceva al synthese de TEM, TEP, e thio-TEP, sed iste compositos, si ben como Myleran e le mustardas de nitrogeno, es efficace primarimente in le morbos del systema hematopoietic.

In le effortio de orientar le effecto antitumoral de agentes alkylante verso le tumor solide (que es un puncto focal in le synthese de proteinas e acidos nucleic), Dopan, i.e. 4-methyl-5-[bis(2-chloroethyl)amino]-uracil, e Sarcolysina, i.e. dl-beta-{p-[bis(2-chloroethyl)amino]phenyl}alanina, esseva synthetisate per combinar le gruppos chloroethylaminic e ethyleniminic con substantias que ha un rolo in processos metabolic. Le duo compositos ha un comparativemente large sprectro antitumoral e un grado considerabile de specificitate in lor effectos contra tumores experimental e clinic. Sarcolysina causa le absorption complete de sarcoma 45 in le ratto e le disparition de seminomas, reticulosarcomas, e tumores de Ewing in le homine. Plure patientes, observate durante periodos de inter un anno e medie e duo annos post le therapia, ha experientiate nulle recurrentia de tumores.

In plus, le synthèse del dipeptidos de Sarcolysina, i.e. de combinationes de Sarcolysina con altere amino-acidos, monstrava que peptidos continente N-formyl-sarcolysina con phenlyalanina e valina retene activitate antitumoral sed perde omne toxicitate.

Assi, le modification del portator del active gruppo chimic, i.e. de di-2-chloroethylamina, per le addition de un serie de biologicamente active compositos aperi un via additional pro le synthese de anticancerose agentes chimotherapeutic.

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# THE RELATIONSHIP BETWEEN HEART DISEASE AND GALL-BLADDER DISEASE \*

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# INTRODUCTION

The purpose of this report is to survey the relationship between heart disease and gall-bladder disease. A review of the American literature will be presented and the physiologic mechanisms in the above relationship will be discussed. The principles of diagnosis and risk of surgery in these patients will be reviewed and illustrative cases presented.

# INCIDENCE

It is well known that the incidence of coexisting gall-bladder disease and heart disease is high in the older age group. The possibility that the coincidence of these diseases is higher than the incidence of each alone has been suggested by a number of authors, 1, 4, 10, 27, 84, 39, 52, 69, 77, 89 though others 41, 59, 78, 76, 81, 87 have stated that this association is simply that of two diseases common to the age group. The evidence, however, seems to favor a close correlation in the incidence of the two diseases. Tennant and Zimmerman 77 conducted a biometric study of 1,600 autopsied cases in 1931 and reported a significant coincidence of the two diseases. Breyfogle 10 and Walsh, Bland, Taquini and White 80 also studied large series of cases and came to the same conclusion.

# HISTORICAL SURVEY

The association between gall-bladder disease and heart disease has been known for many years. Osler <sup>57</sup> described palpitation, distress around the heart, convulsive seizures, and even fatal syncope occurring with acute gall-bladder attacks. Riesman <sup>64</sup> in 1907 called attention to two patients in whom a systolic murmur and increased cardiac dullness had developed during or shortly after an attack of gall-bladder colic. The first systematic study of the problem was a paper by Babcock <sup>1</sup> published in 1909. He reported 13 cases of heart disease which he felt were aggravated by gall-bladder disease, and postulated a reflex inhibition of the heart through vagal stimula-

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tion as one of the possible mechanisms. Other early reports 2, 41, 43, 50, 65, 66, 74, 88 discussed the clinical aspects of the problem of associated heart and gallbladder disease, especially the difficulty in diagnosis. Schrager and Ivy 68 produced respiratory distress by gall-bladder and biliary tract distention in dogs. A number of studies 11, 17, 25, 58, 70, 89 of a similar nature followed. In 1935 Fitz-Hugh and Wolferth 25 reported a group of patients with gallbladder disease who had cardiac symptoms and abnormal electrocardiograms. Some of the electrocardiographic abnormalities reverted to normal following operation. Other clinical reports 8, 6, 14, 16, 56, 60, 73, 89 indicate that, in some patients, improvement of anginal pain or reversion of electrocardiographic abnormalities toward normal may result from removal of a diseased gallbladder. Gilbert and his associates 28, 20, 30 made a series of observations which suggested that distention of the gall-bladder, biliary tree and other abdominal viscera results in decrease of coronary blood flow. Further evidence has been furnished by Ravdin,68 who reported two patients with anginal-type pain prior to cholecystectomy which could be reproduced postoperatively by distention of the common duct through a T-tube.

In recent years the clinical observations fall into three groups: (1) electrocardiographic disturbances produced by gall-bladder disease or biliary tract distention; (2) disorders of cardiac rhythm which improve after cholecystectomy; and (3) the production of anginal-like pain by gall-bladder

disease or biliary tract distention.

Various electrocardiographic abnormalities suggestive of myocardial ischemia, such as inverted T-waves and depressed ST segments, may revert to normal after cholecystectomy for gall-bladder disease. 9, 15, 25, 63 McArthur and Wakefield 46 and Hodge and Messer 85 were able to produce such abnormalities in patients by distention of the common duct through a T-tube. It is important to emphasize that these changes could be induced only if coronary disease was already present. Hodge, Messer and Hill also brought about similar changes in dogs if myocardial damage had previously been produced by coronary ligation or injection of a sclerosing substance. 86

Various arrhythmias disappearing or improving following cholecystectomy have been described in association with cholecystitis.<sup>47, 68, 79</sup> These included ectopic beats, auricular fibrillation, A-V block, complete heart block, and sino-auricular block. In addition, heart block, ventricular tachycardia and cardiac standstill have been produced experimentally by distention of

the bile ducts or other abdominal viscera. 17, 29, 55, 58

The mechanism by which stimuli originating in the gastrointestinal or biliary tract may result in anginal-type pain has been reviewed by Cady, Shallenberger and Koloski 12 and others. 32, 58 They state that stimuli from the gall-bladder or heart may cause substernal or epigastric pain. The heart is innervated by the vagi and sympathetic nerves. The sympathetic fibers originate from cells in the lateral horns of the four upper thoracic segments of the cord, and impulses arising in the heart may be referred

above or below these segments. Both vagal and sympathetic cardiac rami have been demonstrated to be mixed sensory-motor nerves. This is significant, since the ganglion nodosum of the vagus and upper sympathetic ganglion gives rise to axons which course directly to the sensory endings in the heart and coronary arteries. The nerve supply to the gall-bladder is derived from the right vagus and splanchnic nerve through the celiac plexus. Splanchnic nerves ending in the celiac plexus are derived from the sixth thoracic through first lumbar segments in the cord. The great splanchnic nerve has branches which have been traced upward as high as the first or second sympathetic ganglia, and these communicate with the sensory pathways to the heart. Pain resulting from myocardial ischemia usually involves segments from the eighth cervical to the fourth thoracic on the left side, but in both gall-bladder and heart disease, lower segments on the right side may also be the seat of stimuli, and pain may be epigastric in location. Irritation of the gall-bladder may produce anginal-like pain by referral of stimuli to the upper thoracic segments by fibers of the great splanchnic nerve.

The vagal reflexes initiated from the abdominal viscera, including the esophagus, stomach or gall-bladder, are quite important. There is good evidence <sup>16, 18, 28, 29, 80, 82, 42, 40, 55, 71</sup> that these vagal reflexes may produce arrhythmias, cardiac standstill, heart block, and decrease in coronary blood flow. Many of these effects can be blocked by atropine or vagotomy. Banting et al.<sup>24, 48</sup> have reported the production of myocardial damage in dogs by continuous or intermittent vagal stimulation. These effects could be prevented by atropine. Recently, Cullen and Reese <sup>18</sup> employed radioactive Na <sup>24</sup> to demonstrate conclusively in dogs that "rapid distention of the common bile duct with vagus nerves intact lowers myocardial blood flow." They also showed that "when both vagi are cut in the neck, common bile duct distention does not alter myocardial blood flow." Recent articles <sup>5, 61, 78, 81</sup> have reviewed many of these physiologic aspects.

We have found that patients presenting problems involving the heart and gall-bladder usually fall into one of the following five groups: (1) concomitant heart and gall-bladder disease, with arrhythmias which improve after cholecystectomy; (2) concomitant heart and gall-bladder disease, with angina-type pain which improves after cholecystectomy; (3) electrocardiographic abnormalities without other evidence of heart disease, which revert to normal after cholecystectomy; (4) heart disease simulating gall-bladder disease; (5) gall-bladder disease simulating heart disease.

The following case reports will illustrate each type of problem and its management:

## CASE REPORT

Concomitant Heart and Gall-bladder Disease with Arrhythmias Which Improve after Cholecystectomy.

Case 1. This 66 year old woman was admitted to the University of Virginia Hospital on April 4, 1945, with a history of palpitation due to frequent auricular

ectopic beats, and episodes of paroxysmal auricular fibrillation. For four years she had been digitalized and also given quinidine, in an unsuccessful effort to control these archythmias.

Physical examination revealed moderate obesity, and retinal arteriosclerosis with areas of exudate in the macular regions. The heart was not enlarged. No murmurs were heard, and no arrhythmia was present at the time of examination. Blood pressure was 140/100 mm, of Hg. There was no abdominal tenderness, and no masses were felt. The extremities and reflexes were normal.

An electrocardiogram was normal. Gall-bladder x-ray showed the presence of many small stones. A cholecystectomy was done, and pathologic study of the gall-bladder showed chronic cholecystitis and about 24 faceted stones. Convalescence was uneventful. The patient was followed for five years postoperatively, and no further episodes of auricular fibrillation occurred during this time.

Case 2. A 59 year old woman was admitted to the University of Virginia Hospital on February 28, 1952, and discharged on March 23, 1952. For 10 months prior to admission she had had frequent attacks of paroxysmal auricular tachycardia documented by electrocardiogram. These had not been prevented by medications, including digitalis and quinidine. No evidence of organic heart disease was found by history, physical examination or electrocardiogram. A gall-bladder x-ray revealed the presence of stones, and because of the possible precipitation of the attacks of paroxysmal auricular tachycardia by the diseased gall-bladder, a cholecystectomy was performed. The patient gave no history of attacks of cholecystitis or of gall-bladder colic in the past.

Convalescence was uneventful. No further attacks of paroxysmal auricular tachycardia had occurred three years later.

Concomitant Heart and Gall-bladder Disease with Angina Which Improved after Cholecystectomy,

Case 3. This 73 year old woman was admitted to the hospital on March 18, 1954. She gave a history of having had anginal pain for the previous five years, becoming progressively more frequent and more severe. During the six months prior to admission she had had frequent attacks of angina decubitus. Dyspnea, orthopnea and ankle edema developed concurrently. She gave a history of epigastric discomfort and gaseous eructation for two to three years prior to admission, but had not had colicky abdominal pain, vomiting or jaundice.

Physical examination revealed obesity and hypertensive retinopathy. The blood pressure was 170/130 mm. of Hg. On examination of the chest pulmonary râles were heard, and the heart size was indeterminate. There was ankle edema, and the liver was enlarged.

The electrocardiogram showed evidence of myocardial ischemia and left ventricular hypertrophy.

Improvement of the heart failure followed sodium restriction, digitalization and the administration of diuretics, but the angina decubitus persisted. A gall-bladder x-ray revealed many gall-stones. Cholecystectomy was performed, followed by an uneventful convalescence. The angina completely disappeared, and the electrocardiogram showed less evidence of ischemia.

This patient had angina, but few symptoms related to the gall-bladder. However, cholecystectomy was advised and performed because of the possibility that the cholelithiasis was a factor in precipitating the angina. The risk of cholecystectomy was thought to be justified.

Case 4. This 59 year old woman was admitted to the hospital in February, 1955, with a history of substernal pain on exertion, relieved by rest during the five years prior to admission. No symptoms to suggest gall-bladder disease had been elicited

until 24 hours prior to admission, when she developed generalized abdominal pain accompanied by nausea and vomiting.

Physical examination revealed a blood pressure of 190/90 mm. of Hg, cardiac enlargement, tenderness and moderate spasm in the right upper quadrant of the abdomen.

An x-ray of the abdomen showed multiple gall-stones. The electrocardiogram revealed the presence of left bundle branch block.

A cholecystectomy was done and her convalescence was uneventful. The angina disappeared following the operation and had not recurred when the patient was last seen, 18 months later.

Electrocardiographic Abnormalities, Without Other Evidence of Heart Disease, Which Reverted to Normal after Cholecystectomy.

Case 5. This 57 year old woman was admitted to the hospital on November 1, 1948, with a history of four attacks of epigastric cramping pain radiating to the precordial area. Nausea and vomiting were associated, and palpitation occurred concurrently.

Physical examination revealed normal fundi, heart, blood pressure and chest. There was moderate tenderness in the right upper quadrant of the abdomen.

The icterus index was 12. Hemogram and urinalysis were normal. An electrocardiogram (figure 1A) on November 1, 1948, showed T wave changes consistent with myocardial ischemia. Gall-bladder x-ray showed no function.

On November 4 cholecystectomy was performed, and on November 6 and 10 the electrocardiogram showed further changes (figure 1B, C and D). These had reverted to normal by November 20, 1948 (figure 1E), and have remained so since. She has not had symptoms to suggest coronary insufficiency or gall-bladder disease since surgery.

It is probable that by a reflex mechanism the gall-bladder caused a decrease in coronary blood flow which resulted in the electrocardiographic changes, and that, following removal of the gall-bladder, the stimulus which precipitated this reflex disappeared.

Heart Disease Simulating Gall-bladder Disease.

Case 6. This 54 year old white male was admitted to the hospital on October 30, 1952, and discharged on November 28, 1952. He had had gaseous eructations after meals for from three to four years, and on the morning of admission had developed epigastric pain radiating to the right upper quadrant and to the substernal area.

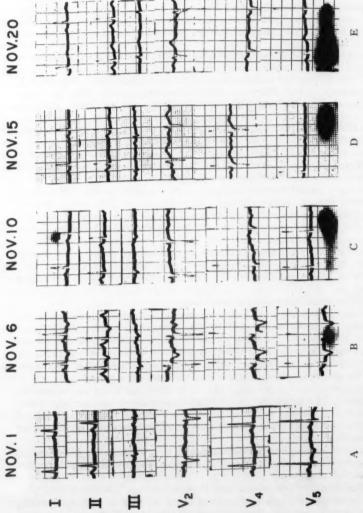
Physical examination revealed tenderness in the epigastrium and in both upper quadrants of the abdomen. The heart and blood pressure were normal.

An electrocardiogram was normal. The white blood cell count was normal on admission, but was 12,000 two days later. Gall-bladder x-ray was normal. Three days after admission, changes developed in the electrocardiogram characteristic of acute myocardial infarction. The patient was given anticoagulants and made an uneventful convalescence.

This patient was thought to have cholelithiasis with cholecystitis, and a normal gall-bladder x-ray was a surprising finding. Further electrocardiographic studies revealed the correct diagnosis.

Gall-bladder Disease Simulating Heart Disease.

Case 7. A 46 year old man was admitted to the hospital on January 31, 1953, with a history of epigastric and substernal pain radiating down both arms, associated with a sensation of dyspnea but not with sweating and not accompanied by nausea or vomiting. This had lasted about one hour, disappeared, and recurred two hours later. He was seen by his family physician, who gave him morphine and advised hospitalization.



Fro. 1. A. November 1, 1948. Electrocardiogram taken on day of hospital admission. T in I, V<sub>4</sub> and V<sub>5</sub> are inverted and are consistent with myocardial ischemia.

B. November 6, 1948. Two days postoperative. T waves have become more deeply inverted in I, V<sub>4</sub> and V<sub>5</sub>, and negative T waves have appeared in II, III and V<sub>5</sub>, probably indicating more marked ischemia.

C. Six days postoperative. T waves are flattened in I, II, III and V<sub>6</sub>, and less inverted in V<sub>4</sub>.

D. T waves have returned toward normal in all leads.

E. T waves have become upright and electrocardiogram is normal.

Physical examination revealed moderate obesity. The blood pressure was 165/90 mm, of Hg. The heart sounds were normal; no rub or murmur was heard. The abdomen was negative.

No leukocytosis or temperature elevation occurred, and the sedimentation rate remained normal. Three electrocardiograms were normal. The patient had an episode of similar pain after admission. After five days he was discharged from the hospital with a diagnosis of coronary arteriosclerosis with coronary insufficiency.

The patient had no further trouble until June 7, 1954, when he developed epigastric pain associated with nausea and vomiting. Shortly after onset the pain became most marked in the right upper quadrant and was associated with tenderness and spasm in this area.

Physical examination was otherwise normal. The white blood cell count was 16,500. Temperature was 100° F. Two electrocardiograms were normal. The gall-bladder x-ray showed no shadow. A diagnosis of acute cholecystitis was made, and cholecystectomy was performed on January 9, 1954. Pathologic study of the gall-bladder showed subacute cholecystitis with cholelithiasis. The patient had an uneventful convalescence and had no further symptoms. The electrocardiogram remained normal.

This patient was seen by several physicians, who concurred in the diagnosis of coronary insufficiency in 1953. When he returned in 1954, the clinical picture was typical of cholecystitis, and there appears to be no doubt that the original attack, in 1953, was a manifestation of cholelithiasis rather than coronary artery disease. He was seen two years later and had had no further symptoms.

Case 8. This 62 year old man developed substernal pain on October 7, 1956, and was admitted to the hospital. A diagnosis of acute myocardial infarction was made and confirmed by an electrocardiogram (figure 2A, B). He made an uneventful convalescence and was discharged on October 30 by ambulance with instructions to limit his activities markedly for the next six weeks.

The patient developed right upper quadrant pain on November 25, 1956, associated with nausea and vomiting. There were tenderness and spasm in the right upper quadrant. Physical examination was otherwise negative. An electrocardiogram showed changes suggestive of a recent myocardial infarction, but when this was compared with the previous electrocardiograms it was noted this represented incomplete regression of the previous electrocardiogram. The temperature was 99° F. and the white blood cell count 12,600, with increase of the polymorphonuclears on the differential. A gall-bladder x-ray on November 27 and November 29, 1956, revealed no gall-bladder shadow.

Convalescence was uneventful. The physical signs and symptoms disappeared. The white blood cell count returned to normal, and the patient was discharged on December 1, 1956. Subsequent electrocardiograms showed no changes and were very suggestive of a ventricular aneurysm. This was found to be present fluoroscopically. The patient was seen in the office on December 14, 1956, with no symptoms. The electrocardiogram taken at that time is shown in figure 2D.

This man had an aneurysm of the left ventricle resulting from a myocardial infarction, with residual electrocardiographic changes resembling those of acute anterior infarction. The gall-bladder attack was typical clinically, but without the knowledge that an infarction had occurred previously one might have concluded that the pain associated with the electrocardiographic changes represented myocardial infarction.

In an individual with a ventricular aneurysm the differential diagnosis between myocardial infarction and gall-bladder disease may pose a particularly difficult problem.

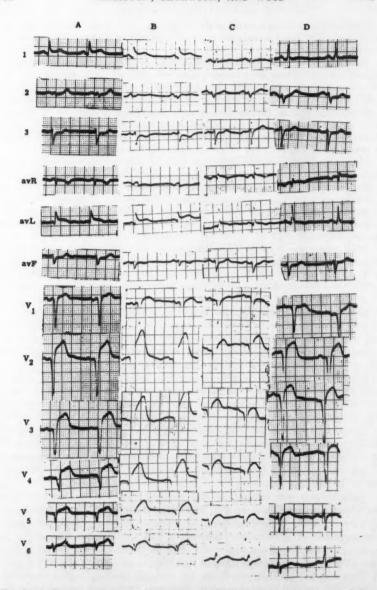


Fig. 2. A. Electrocardiogram taken on October 7, 1956. This shows changes indicative of a recent anterior myocardial infarction.

B. Electrocardiogram taken on October 13, 1957. A small Q wave has appeared in  $V_0$ , perhaps indicating extension laterally, though this change may be due to slight difference in placement of the electrodes.

C. Electrocardiogram taken on November 27. Two days after onset of acute cholecystitis. The ST segments in AVL,  $V_1$ ,  $V_2$ ,  $V_3$ ,  $V_4$  and  $V_5$  are elevated. There is a significant

# DISCUSSION

The differential diagnosis involving upper abdominal and lower chest pain may be quite puzzling. Friedberg,26 Levine 40 and others 86 have stressed the clinical occurrence of biliary disease and heart disease in the same patient. Digestive symptoms are not uncommon in angina pectoris, 13 and pain of gastrointestinal origin may simulate angina pectoris.3, 8, 37 Nothing replaces a painstaking and detailed history concerning the chest pain. The classic association of angina pectoris with exertion is very helpful, as this is quite unusual for gall-bladder pain. The latter often begins at night, and upper abdominal residual tenderness of gall-bladder colic may persist for several days. The Master two-step test 81 and the ballistocardiogram 19, 20 may also be helpful in deciding the part coronary artery disease is playing in the clinical picture. Smith and Larkin 12 have employed sympathetic nerve block with procaine to differentiate abdominal pain from cardiac pain when it appeared that an acute abdominal surgical emergency might be present. It seems wise to study the gall-bladders of all patients with angina because of the probability that gall-stones, if 'present, potentiate the anginal symptoms by a trigger mechanism.

The increased hazard of surgery in the cardiac patient is well known. The mortality of major surgery in patients with coronary artery disease has been previously reported to vary from 5.3% to 14.3%; 33, 44, 45, 54 however, recent studies indicate that these findings are too high, and that with improvement both in preoperative and postoperative care and in anesthesia, and closer coöperation between surgeon and internist, the mortality can be reduced to below 3%. 61, 38, 23

A recent myocardial infarction will increase the mortality considerably, and surgery should be deferred if possible for four months.<sup>21</sup> Myocardial infarctions in the immediate postoperative period have been reported,<sup>3, 67, 81</sup> and some authors <sup>67, 81</sup> advise postoperative electrocardiograms before ambulation because of the likelihood that this might have occurred unexpectedly. Age alone is not a contraindication to elective biliary tract surgery, but the elderly patient tolerates emergency biliary surgery poorly,<sup>31, 75</sup> and, when possible, cholecystectomy should be an elective operation.

Anesthesia is another vital feature in surgery of this group of patients. There should be close coöperation between internist, surgeon and anesthetist. Vagolytic agents should be given preoperatively, and shock and hypoxia carefully avoided.

The selection of patients for cholecystectomy in the hope of improving

Q wave in AVL, and QS complexes are present in  $V_{1}$ ,  $V_{2}$ ,  $V_{8}$  and  $V_{4}$ . These changes are similar to though not exactly like those seen in A. These are consistent with a recent infarction or a ventricular aneurysm.

D. Electrocardiogram taken December 13, 1956. When the patient returned for an office visit there were no symptoms. There are no essential changes as compared with the previous electrocardiograms.

or alleviating heart disease must be highly individualized. There must be good clinical evidence to implicate the biliary system as a contributory factor to symptomatology of heart disease. Patients with gall-stones, single or multiple, and angina pectoris or uncontrollable arrhythmias, should have cholecystectomy because of the possibility of beneficial effect on the heart disease, as well as the potential hazard of the gall-stones per se. An acute surgical condition might develop which would require operation under unfavorable circumstances and result in a greater risk than if it was done electively.

Patients with a history of repeated attacks of cholecystitis who have a nonfunctioning gall-bladder on x-ray should also have a cholecystectomy, for the same reasons.

Patients with an asymptomatic, nonfunctioning gall-bladder should not have such surgery unless more clinical evidence indicating gall-bladder disease develops.

A few conclusions seem warranted from a review of the apparent association of heart disease and gall-bladder disease:

- 1. Heart disease and concomitant gall-bladder disease are quite common. An association greater than coincidence is probable.
- 2. Experimental and clinical evidence has shown that arrhythmias and decreased coronary blood flow may be induced by distention of the biliary tract.
- 3. Angina pectoris, arrhythmias and electrocardiographic abnormalities may improve after cholecystectomy. Electrocardiographic changes which revert to normal after operation appear to constitute evidence of underlying coronary artery disease.
- 4. The mortality risk in patients with heart disease and gall-bladder disease is probably under 3%. Elective cholecystectomy is usually well tolerated.
- 5. Improvement in cardiac status results only from removal of extrinsic stimuli. There is no change in the fundamental, intrinsic heart disease.

### SUMMARY

- 1. The statistical incidence of heart disease and gall-bladder disease is presented and discussed.
- 2. Some of the literature on the subject is surveyed, and evidence is cited to support the view that the gall-bladder may initiate reflexes which help to produce electrocardiographic changes, arrhythmias and an anginal-type pain.
  - 3. The differential diagnosis and physiologic mechanisms are reviewed.
- 4. The risk of biliary surgery in the patient with heart disease is cited, and indications and contraindications are discussed.
  - 5. The types of problems encountered are illustrated with case reports.

#### SUMMARIO IN INTERLINGUA

Studios statistic pare indicar un signification del coexistentia de morbo de vesica biliari con morbo cardiac, a judicar per un revista del litteratura. Le entitates cardiac del quales il se tracta particularmente es morbo de arteria coronari e varie arrhythmias, incluse pulsos ectopic, fibrillation auricular, e bloco cardiac. Post le elimination del vesica biliari, il es reportate que iste arrhythmias dispare o se attenua in lor frequentia, durante que le symptomas de insufficientia coronari se meliora.

Es opinate que le conditiones mentionate resulta de reflexos vagal que es initiate in le vesica biliari con consequente reductiones del fluxo coronari.

Dolores que ha lor origine in le vesica biliari pote referer se al thorace e simular dolor anginal. Similemente, dolores causate per insufficientia coronari pote radiar verso le abdomine e simular morbo de vesica biliari. Iste phenomenos es le effecto de un distribution inusual del circuitos de transmission de dolor in certe individuos.

Es reportate casos illustrative del disparition o melioration de varie anormalitates cardiac post le effectuation de cholecystectomia. Le anormalitates includite es fibrillation auricular, tachycardia auricular paroxysmal, angina de pectore, e indicationes electrocardiographic de ischemia myocardial. Es etiam presentate casos que illustra morbo cardiac simulante morbo de vesica biliari e alteres que illustra morbo de vesica biliari simulante morbo cardiac.

Le intervention chirurgic es a recommendar quando on ha un prova definite de morbo de vesica biliari coexistente con arrhythmias o angina sed non in casos in que signos roentgenographic de dysfunction del vesica biliari suggere solmente cholecystitis.

Le mortalitate per cholecystectomia in iste patientes es circa 3% o minus si le operation es effectuate como mesura elective.

Le melioration del stato cardiac resulta ab le elimination de stimulos extrinsec. Nulle alteration del cardiopathia intrinsec es effectuate.

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# **TOBACCO HYPOGLYCEMIA\***

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Tobacco smoking and its good or bad effects on the smoker have created much controversy in recent years. A significant but little-known fact is that tobacco smoking has been shown to produce symptomatic hypoglycemia which disappears when smoking is stopped. Since 1946 we have seen 24 patients with tobacco hypoglycemia, which indicates a closer association between tobacco usage and hypoglycemia than has been generally recognized. The diagnosis may be established with reasonable certainty in an internist's office, and can be confirmed by the rapid relief of symptoms following the withdrawal of tobacco. We found there was no longer a hypoglycemic curve in those patients from whom we obtained a recheck glucose tolerance test two years after abstinence from tobacco usage.

The average glucose tolerance curve and the principal symptoms are

# AVERAGE OF 24 HYPOGLYCEMIC PATIENTS ON INITIAL GLUCOSE TOLERANCE TEST

Average blood sugar of 24 tested patients is lowest 3 1/2 hours after oral glucose. Note the rise at 4 and 5 hour intervals.

#### CHART 1.

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TABLE 1 Symptoms in Order of Frequency

Symptoms	Cases	Per Cent
Nervousness	23	95%
"Dizziness"	22	90%
Fatigue	22	90%
"Blind staggers"	18	75%
Headache	15	60%
"Fainting"	12	50%
Cough	4	16%

shown in chart 1 and table 1. We have made the diagnosis of tobacco hypoglycemia only in those patients who met all of the following criteria:

- 1. The use of one or more packages of cigarettes a day (or equivalent).
- 2. Symptoms compatible with the diagnosis of hypoglycemia.
- 3. Blood sugar \* below 55 mg. per 100 c.c., concurrent with the above symptoms.
- 4. Prompt relief by the ingestion or administration of glucose at the time symptoms occurred.
  - 5. Complete and permanent relief of symptoms with cessation of smoking.

Since the most important point in the diagnosis is to establish the fact of a pathologically low blood sugar level in the presence of symptoms, the means for accomplishing this most consistently deserves some comment. Analysis of blood during spontaneous "attacks" or after prolonged fasting can confirm the association of symptoms with significantly low blood glucose. Blood withdrawn during an episode of spontaneous symptoms cannot be depended upon to establish this relationship regularly. Apparently, from our experience, the lowest levels of blood sugar occur at the onset of symptoms. There is an almost completely unavoidable delay in obtaining a blood specimen during the "attack." Many attempts to demonstrate low blood sugar levels in these patients after 15 and 39 hours of fasting have been unsuccessful. This may be an important diagnostic point in differentiating between tobacco hypoglycemia and functioning islet cell tumor.

Oral glucose tolerance curves, using 100 gm. of glucose 15 hours after a light evening meal, demonstrated abnormally low blood sugars at the time symptoms were produced in all patients reported here. This method of establishing correlation of symptoms and laboratory confirmation had added value because the patient was under observation. As soon as blood was drawn we could give sugar when indicated and note its effect.

Initial and follow-up glucose tolerance curves are shown, with discussion of clinical features of the following typical cases:

### CASE REPORTS

Case 1 (figure 1). A white male, age 65 when first seen in February, 1946, stated he had hypoglycemia and was planning to follow his physician's advice to have

\*Blood sugar was estimated by the method of Folin and Wu. Venous blood was used.

Glucose Tolerance

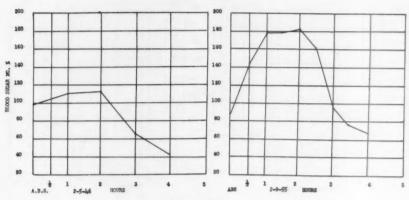


Fig. 1.

an operation to obtain relief. He had begun to have attacks of dizziness, sweating and unconsciousness in 1931. These episodes had gradually increased in frequency and severity, occurring several times daily, so that since 1944 he had been practically disabled. He had smoked for 40 years, as much as two and one-half packages of cigarettes a day. In the 1946 glucose tolerance curve, when the blood sugar was at 42 mg.%, he had blurring of vision, palpitation, tremor and extreme apprehension. These were relieved in three minutes by the feeding of sugar. He was advised to stop smoking and did so at once. One week later he had a single mild attack. Except for this he has had no recurrence of any kind.

Case 2 (figure 2). A white male politician, age 46 when seen in January, 1947, had had attacks for one year of dizziness, apprehension and fear of falling. He had smoked cigarettes for 28 years, up to one and one-half packages daily. When his blood sugar fell to 33 mg.% in the third hour of the test he had a severe attack, which

Glucose Tolerance

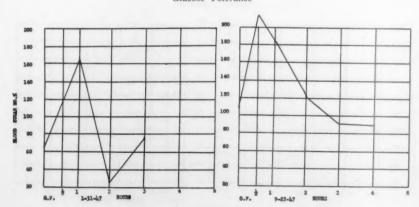


Fig. 2.

Glucose Tolerance

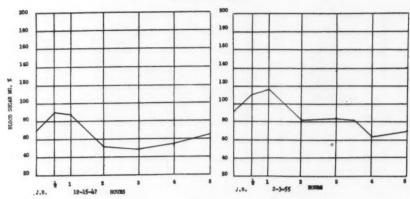


Fig. 3.

was promptly relieved when he ate candy. He stopped smoking in January, 1947, and has been entirely well.

Case 3 (figure 3). A white male car dealer, age 43 when seen in December, 1947, had smoked one package of cigarettes daily for 25 years. He complained of severe dizziness, lightheadedness, fear of falling, and blurring of vision, especially when walking in crowds. When his blood sugar was 48 mg.% (shown on the 1947 curve), these symptoms were reproduced. Prompt relief followed drinking sweetened orange juice after completion of the test. He stopped smoking in December, 1947, and his symptoms ceased. He resumed smoking in May, 1948, and in nine months his symptoms recurred. He stopped for the second time in August, 1949, and was again relieved. He has not smoked and has not had symptoms since that time.

Case 4 (figure 4). A white male violin maker, age 44 when first seen in February, 1948, had had attacks for about six months of dizziness when walking, blurred vision, and a feeling that he might fall. This was accompanied by weakness, pound-

Glucose Tolerance

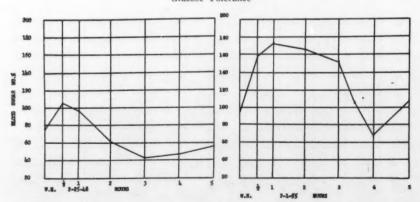


Fig. 4.

# Glucose Tolerance

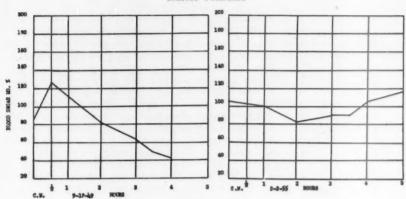
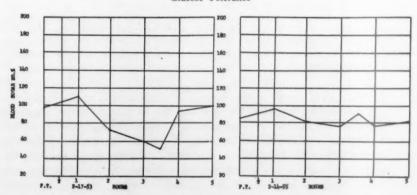


Fig. 5.

ing of his heart, perspiration, tremor and apprehension. He was afraid to walk around the block, and had stopped working because of tremor and nervousness. He had gradually increased his smoking during 26 years to more than a package of cigarettes and three or four cigars a day. During the 1948 glucose tolerance test he had a severe attack when the blood sugar was 43 mg.%. He stopped smoking in February, 1948, and his trouble subsided. He has been able to work and has had no symptoms of this kind since June, 1948.

Case 5 (figure 5). A white male, age 55 when seen in September, 1949, had smoked two packages of cigarettes daily for 30 years. He had had a few minutes of aphasia in 1935, followed by repeated dizzy spells and chronic cough. When his blood sugar fell to 41 mg.% he exhibited dizziness and fright. After he stopped smoking in September, 1949, complete relief of symptoms resulted at once and did not recur. He died of acute myocardial infarction in October, 1955. At autopsy, serial sections of the pancreas revealed a normal organ, and careful search revealed no evidence of aberrant pancreatic tissue.

## Glucose Tolerance



Frg. 6.

Case 6 (figure 6). A white female, age 24 when first seen in February, 1953, had smoked up to two and one-half packages of cigarettes a day for nine years. She had been having attacks of dizziness and weakness, with fright, palpitation and severe aching over her entire body. She found that her symptoms were relieved by drinking Coca Cola, and was using 10 to 12 bottles a day. She had her usual symptoms when the blood sugar was 52 mg.% during our test. She stopped smoking completely in February, 1953, and has had no symptoms since.

Case 7 (figure 7). This case illustrates a patient with hypoglycemia who did not stop smoking. He meets the other four criteria but is not included in the 24 patients we are reporting as proved cases. A white male merchant, age 47 when first seen in February, 1947, had smoked more than a package of cigarettes a day for 29 years. He had had spells of fuzzy headaches, weakness, and difficulty in concentrating for 20 years. At times the symptoms occurred several times a day; at other times he had only two or three attacks a week. The attacks had been increasing in severity in the last four years, and were accompanied by perspiration, tremor and great uncertainty. He was advised to have a glucose tolerance test, which he failed to do

Glucose Tolerance

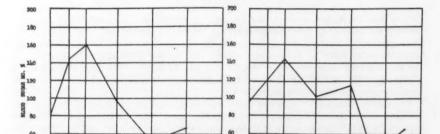


Fig. 7.

until 1950. At the time of the test the typical symptoms plus low blood sugar were reproduced simultaneously. He was then advised to stop smoking, but instead he consulted a psychiatrist, who told him he had never heard of tobacco causing trouble of this kind. The patient reduced his smoking to 15 cigarettes a day, and has been smoking filtered cigarettes for two years. He continues to have the same spells with about the same frequency.

# DISCUSSION

The symptoms manifested by these patients were remarkably similar to those seen with overdoses of long-acting insulin. Although the symptoms never occurred immediately after eating, there usually was no history of spells occurring solely after hours of fasting. The degree of cerebral disturbance was variable. Some patients experienced mental confusion, syncopal symptoms and amnesia for as long as one hour. We saw no patient with a convulsion. Almost without exception, the patients were apprehensive, unstable emotionally and insecure. A striking feature was the fear

of falling and fear of becoming unconscious. Many patients used the term "blind staggers" in the description of their attacks, intending to convey the lightheaded feeling of impending loss of consciousness and blurring of vision, with incoördination and unsteady gait. Most of these individuals held on to a table, chair or other object while the spells lasted, the time varying from a few minutes to three hours. We had the opportunity of observing the symptoms of all of these patients, the "attack" being either spontaneous or induced during the glucose tolerance test. In every case, symptoms subsided within five minutes after taking a sweetened drink or food.

We insisted that our patients stop the use of tobacco altogether and at once. In every patient who gave up tobacco completely the symptoms subsided, usually dramatically and simultaneously with the cessation of smoking. In one instance only (case 4) the patient required two months for complete relief, and it was suspected, but not proved, that the tobacco habit was not immediately conquered. Two patients resumed smoking after abstinence for several months, and in each case the hypoglycemia recurred in about six months. Both patients gave up smoking for the second time, after which their symptoms again subsided dramatically.

It is of interest to note that one man with hypoglycemia who was a heavy smoker was completely asymptomatic for five years after he stopped smoking. He then had one moderately severe attack after nearly 24 hours without food. Interestingly enough, his follow-up glucose tolerance curve is the only recheck test which shows hypoglycemia in a patient who had stopped smoking. This patient may have something which is not tobacco hypoglycemia, and he has not been included in this series.

The mechanism by which hypoglycemia can be produced by the use of tobacco is unknown. A moderate rise of blood sugar due to smoking has been demonstrated, and it is possible that repeated smoking could eventually produce exhaustion of the supply of available glucose and glycogen in the body. However, our own repeated observations have failed to show a consistent increase of blood sugar after smoking two cigarettes in rapid succession. This matter deserves further study.

Spontaneous hypoglycemia has usually been grouped in three etiologic categories: functional, hepatic and pancreatic (or surgical). Just where the hypoglycemia which results from tobacco smoking can be correctly placed is not clear.

Functional hypoglycemia occurs principally in women, and tobacco hypoglycemia predominantly in men. It would be interesting to study again the patients previously reported as functional for incidence of smoking and, if possible, for effects of stopping the use of tobacco.

Hepatic hypoglycemia is a possibility in some of our patients, since the use of alcohol is admitted by most of them. However, no patient had evidence, either historically or clinically, of serious liver disease. There has been no report, to my knowledge, that patients with hypoglycemia due to liver disease have been relieved of symptoms by discontinuing tobacco.

There are several hundred reported cases where islet cell adenomata have been attacked surgically. Many of these cases have been unequivocally neoplastic, with relief of symptoms following removal. Whether others, histologically benign, or of the so-called "hypertrophy of islands" type, could have resulted from an abnormal stimulus to insulin production, and therefore represent a phase of compensatory hypertrophy, is at least an interesting speculation. However, if it is possible that tobacco could be the stimulus for producing islet cell hypertrophy and hyperfunction in some of these patients, it would appear logical to withhold surgery for hypoglycemia in smokers until they have stopped smoking for a few days or longer. The possible relationship between this syndrome, islet cell tumors and intractable peptic ulcer also warrants consideration.

#### SUMMARY AND CONCLUSIONS

1. The incidence of hypoglycemia associated with the use of tobacco is about 0.2% of patients in our practice.

2. The condition occurs in individuals who apparently are peculiarly sensitive to some substance found in tobacco smoke, the most likely being nicotine.

3. Although the great majority of patients with functional hypoglycemia are women, 22 out of 24 cases of tobacco hypoglycemia reported here occurred in men.

4. Tobacco hypoglycemia is a clinical entity which should be considered in the differential diagnosis of patients with evidence suggestive of either islet cell hypoglycemia or so-called functional hypoglycemia.

#### SUMMARIO IN INTERLINGUA

Experientias con 24 patientes, durante le annos depost 1946, demonstra un definite association inter le fumar de tabaco e le presentia de hypoglycemia symptomatic. Le diagnose pote esser effectuate al sala de consulta del medico e se confirma per le rapide alleviamento que seque le abstention ab tabaco. Nos ha diagnosticate hypoglycemia a tabaco solmente in patientes qui satisfaceva omne le sequente criterios:

- 1. Uso de un pacco de 20 cigarrettas per die o plus, o le equivalente.
- 2. Symptomas compatibile con hypoglycemia.
- Sucro de sanguine infra 55 mg per cm<sup>8</sup>, concurrente con le symptomas supramentionate.
- Prompte occurrentia de alleviamento per le ingestion di glucosa quandocunque le symptomas occurre.
- Alleviamento complete e permanente del symptomas quando le fumar esseva discontinuate.

Le plus importante puncto diagnostic es le demonstration de un pathologicamente basse nivello del sucro sanguinee in le presentia de symptomas. Nos ha trovate que le nivello del sucro sanguinee es le plus basse al tempore del declaration de symptomas, e nostre plus uniformemente accurate mesura diagnostic es un test del tolerantia pro glucosa, effectuate con 100 g de glucosa 15 horas post un leve repasto vespertin. Omne le patientes includite in le presente reporto demonstrava anormalmente basse

nivellos del sucro sanguinee al tempore quando le symptomas se manifestava. Iste methodo es specialmente profitabile proque le patiente se trova alora sub le observation del medico. Le symptomas pote esser correlationate con le confirmation laboratorial, e quando specimens de sanguine es obtenite, il es possibile administrar sucro e notar le effecto.

Tests del sucro de sanguine que es effectuate durante attaccos spontanee o inter 15 e 39 horas post jejunation non produce resultatos uniforme. Iste constatation es possibilemente un puncto de signification diagnostic in differentiar inter hypoglycemia a tabaco e le presentia de un functionante tumor de cellulas de insula.

Symptomas nunquam occurreva immediatemente post le ingestion de nutritura, sed—del altere latere—illos non occurreva exclusivemente post horas de jejunation. Illos esseva remarcabilemente simile al symptomas vidite post le uso de doses excessive de insulina a action prolongate. Le patientes se sentiva apprehensive, emotionalmente instabile e insecur, e le plus frappante observation esseva lor timor de cader e de perder conscientia. Le disturbationes cerebral variava. Plures del patientes experientiava confusion, syncope, e amnesia durante periodos de usque a un hora. Nulle convulsiones esseva vidite. Omne le patientes esseva observate durante "attacos" spontanee o inducite, e in omne caso le symptomas subsideva intra cinque minutas post le ingestion de sucrate nutrimento o bebita.

Le patientes recipeva le instruction de cessar lor fumar immediatemente e completemente. In omne le casos in que le patientes observava le instruction, le symptomas subsideva, in le majoritate del casos dramaticamente e promptemente.

Como il es possibile que hypoglycemia es producite per le uso de tabaco, remane indeterminate, e le question merita studios additional. Le correcte categoria etiologic in le qual hypoglycemia a tabaco debe esser placiate es etiam non jam clar.

Nos ha nulle prova que indicarea que tabaco es un factor in le production de hypoglycemia hepatic, sed le possibilitate de su presentia debe esser prendite in consideration in casos de "hypoglycemia functional" e quando on pensa al intervention chirurgic pro "adenoma a cellulas insular." Le relation possibile inter hypoglycemia a tabaco, tumor a cellulas insular, e intractabile ulceres peptic merita esser investigate.

Le incidentia de hypoglycemia a tabaco amontava a circa 0,2% del nove patientes. Novanfa pro cento del casos esseva vidite in masculos.

Le condition occurre in individuos qui es apparentemente sensibile pro alicun ingrediente de tabaco. Iste ingrediente es probabilemente nicotina.

Hypoglycemia a tabaco es un entitate clinic que merita prendite in consideration in omne casos de hypoglycemia "functional" o "chirurgic."

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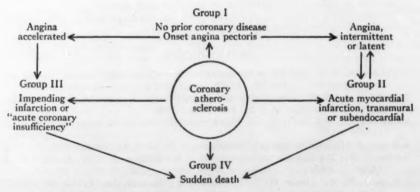
# VIRTUE OF PROMPT ANTICOAGULANT THERAPY IN IMPENDING MYOCARDIAL INFARCTION: EXPERIENCES WITH 318 PATIENTS DUR-ING A 10-YEAR PERIOD\*

By E. Sterling Nichol, M.D., F.A.C.P., William C. Phillips, M.D., and Gus G. Casten, M.D., Miami, Florida

THE clinical pattern of coronary atherosclerosis is remarkably variable in different subjects, but observation over a period of years reveals that patients fall into groups delineated by the clinical progression of the disease, as depicted in the diagram below.

1. Patients with no previous signs of coronary disease who develop angina pectoris with or without detectable trigger factors such as smoking, dietary excess, gall-bladder disease, hiatal hernia or emotional stress. Some of this group go along well stabilized for years without obvious progression of their coronary disease, with intermittent pain modified by avoiding trigger mechanisms, restriction of activities, the use of sedatives, ataraxic agents and coronary dilators.

2. Patients with no previous signs of coronary disease, as well as patients from group 1 who without warning, develop transmural or subendocardial myocardial infarction. The acute attack may prove fatal, or recovery may take place and be followed for a variable interval by angina pectoris or congestive heart failure or an indefinite period free of any cardiac



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complaint. Eventually, in many, another attack of acute myocardial infarction occurs.

3. Patients who manifest the preinfarction syndrome, with or without earlier signs of coronary atherosclerosis or myocardial infarction. Our experiences with prompt use of heparin and oral anticoagulants to forestall myocardial infarction in such patients make up the present study.

4. Patients from any of the above groups who may develop ventricular

fibrillation or cardiac standstill and die suddenly.

Patients classed as "impending infarction" or one of the "intermediate syndromes" may later exhibit a stabilized or latent intermittent anginal syndrome. Patients with full-blown myocardial infarction may, after survival, be free of anginal symptoms or experience recurrent attacks of angina pectoris, one of which may again eventuate in myocardial infarction. above diagram portrays the variable clinical phases developing during the natural history of coronary atherosclerosis.

It is high time to discard our classic descriptions of angina pectoris. Anginal pain starts abruptly and usually last only a few minutes. As brevity is the soul of wit, it surely is the sole dimension of angina pectoris. The run-of-the-mill case does not describe severe retrosternal pain, but only moderate pressing or constricting anterior chest discomfort, sometimes "choking" in character. When there is radiation of pain to the left arm or wrist it may be extraordinarily severe or knifelike, whereas interscapular pain is usually boring or dull. Angina is rarely associated with angor animi or profuse sweating. It is often, but not invariably, precipitated by anything which increases cardiac work, such as walking or emotional disturb-"Status anginosa" is a hand-me-down term from the days when the difference between angina pectoris and acute myocardial infarction was not appreciated, and there is no reason for retaining this term.

# DIAGNOSIS OF IMPENDING MYOCARDIAL INFARCTION

That some attacks of acute myocardial infarction are foreshadowed by premonitory signs was pointed out by Wearn in 1923,1 Kahn 2 in 1926 and others.<sup>8, 4, 5</sup> This prodromal state was more clearly depicted in 1937 by Feil and Sampson and Eliaser. Within the last few years Yater et al.,8 Mounsey 9 and Maurice and co-workers 10 have added to our knowledge of this clinical phase in patients with coronary atherosclerosis. Reeves and Harrison 11 recently stated: "In many patients with angina pectoris a progressive increase in the frequency of the episodes, under the same or decreased work load, denotes imminent myocardial infarction." It is now generally agreed that a substantial proportion of all attacks of acute myocardial infarction is ushered in by premonitory anginal pain recurring in varying degree over a span of hours, days or weeks before the major blow The diagnosis of impending infarction is made on clinical, not pathologic grounds. The varied prodromal signs of infarction consist of

(a) onset of angina pectoris for the first time not controlled readily by rest, sedation and coronary dilators; (b) reactivation of anginal pain after a long quiescent period; (c) abrupt decrease in tolerance for physical activity in patients with stabilized angina; (d) increased severity and frequency of anginal pain in patients lacking extracoronary trigger factors to explain the worsening angina; (e) radiation of anginal pain to a new site, such as the back, jaw or both arms, instead of the customary substernal or left arm radiation; (f) new features associated with pain, such as excessive diaphoresis, nausea, or a sense of impending dissolution; (g) angina decubitus as a new development, occurring particularly in the early morning hours, or forceful recurrence after a substantial free interval (nocturnal pain recurring during the same night is particularly significant); (h) decreased relief of pain afforded by a dose of nitroglycerin that was previously effective.

One or more of these signs characterize the stage of progressive coronary atherosclerosis called "impending" or "threatened" myocardial infarction, or the "pre-infarction syndrome." The alteration in the pattern of previously stabilized angina pectoris is often clear-cut and sometimes dramatic; the diagnosis rests squarely on the patient's story. A new constellation of coronary symptoms not explained by extracoronary trigger factors and not accompanied by signs of infarction suggests impending infarction.

# PHYSIOLOGIC AND PATHOLOGIC CONCEPTS

Clinicians are familiar with the morphologic changes found in well defined transmural infarction or in a ringlike, confluent, subendocardial infarction, but the pathologic counterpart in the clinical realm lying between angina pectoris and myocardial infarction is often vaguely conceived. Necropsy studies 9 suggest that increasing myocardial ischemia due to gradual atherosclerotic closure of a coronary artery often accounts for prodromal signs. Protracted ischemia, if severe, leads to gross infarction, but lesser degrees of ischemia produce focal necrosis, i.e., clusters of dead cells in the myocardium. When the electrocardiographic signs of myocardial ischemia persist for more than a few hours, whether or not accompanied by slight leukocytosis or acceleration of the sedimentation rate or increase in C-reactive protein or serum transaminase, the clinical phase should be considered to have a pathologic or structural basis, i.e., myocardial necrosis of some degree. The terms "myocardial ischemia" and "miliary" or "disseminated focal myocardial necrosis" have been used interchangeably by some authors. "Ischemia" is the functional state of reduced blood supply to the myocardium, and "necrosis," even if confined to one focal cluster of myocardial cells, is a structural injury. (Extensive myocardial necrosis or infarction is often followed by subsidence of anginal pain, which substantiates the concept that anginal pain is due to ischemia, not to necrosis.) The delineation between isolated "focal necrosis" and areas of patchy or disseminated focal necrosis ranking grossly as "subendocardial infarction" is not well defined, and often

TABLE 1

Terminology Used Concerning Coronary Atherosclerosis

Physiologic or Symptomatic State

Angina pectoris
Myocardial ischemia, transient or prolonged
Coronary insufficiency (acute, or chronic)
Coronary failure
Intermediate coronary syndrome
Slight coronary attack
Impending infarction (pre-infarction syndrome)

#### Pathologic or Structural State

Coronary atherosclerosis and narrowing Focal or patchy myocardial necrosis Minor myocardial infarction Subendocardial infarction—disseminated necrosis\* Transmural myocardial infarction\*

\* With or without acute coronary occlusion.

the symptomatic state cannot be adequately correlated with the extent of structural injury. Our clinical-pathologic concepts of the states lying between "physiologic ischemia" and "gross infarction" are further clouded by the electrophysicist, who speaks of both "zone of ischemia" and "zone of injury," as well as of "necrosis of infarction." Table 1 sets forth the variable terminology used in current cardiologic literature concerning various phases of coronary atherosclerosis.

The term "acute coronary insufficiency," rather widely accepted because of the numerous papers of Master and co-workers 12 appearing between 1941 and 1950, is physiologic, and its implied pathologic counterpart is focal or disseminated myocardial necrosis, usually subendocardial. Master, although frankly admitting the inadequacy of the term, has sought to establish the concept of acute coronary insufficiency as a pathologic and clinical entity; but the term refers to the development of a disproportion between the available coronary blood flow and the needs of the myocardium, i.e., prolonged myocardial ischemia. When first described, it was stressed that precipitating factors such as surgery, hemorrhage, shock, pulmonary embolism or severe physical or emotional stress accounted for most cases, and little mention was made of "spontaneous" cases. It was pointed out that coronary occlusion was not an associated finding, a fact which could be ascertained only at necropsy, as noted by Freedberg et al.13 Master and his associates stated that "acute coronary insufficiency" was such a benign clinical state that anticoagulant therapy was not indicated, but they did not present a detailed follow-up study of patients. In 1951 Master and Jaffe 14 acknowledged that at the outset "acute coronary insufficiency" may be mimicked by the pre-infarction syndrome, and by this time less emphasis was placed on the provocative factors, and more cases of "spontaneous" acute coronary insufficiency (50%) were observed. It is pertinent to quote from these authors: "During the first few days of an acute coronary episode it may be difficult for the physician to distinguish between acute coronary insufficiency

and the premonitory phase of coronary occlusion. Almost half the patients with coronary occlusion experience premonitory pain for days or weeks during which period the electrocardiographic pattern of coronary insufficiency, that is, RS-T depression and T-wave inversion, may be present. At this time, it is impossible to foretell whether the condition will subside or lead to occlusion with through and through infarction." Rosenbaum, Wilson, and Johnston <sup>15</sup> pointed out in 1945 that "some of the attacks of pain which have usually been considered prodromal symptoms of myocardial infarction actually represent the development of a small anteroseptal infarct, and that the more characteristic symptoms of acute coronary thrombosis which often occur later are due to an extension of this initial lesion. The true situation must be recognized, if such patients are to be properly treated."

Scherf <sup>16</sup> pointed out the inadequacy of the term "coronary insufficiency" to connote a clinical state, and emphasized, with reference to worsening angina pectoris, "It is impossible to state whether we are dealing with the premonitory syndrome preceding coronary thrombosis or whether an infarction or several small infarctions exist. *Prolonged observation usually will supply the answer.*" Kory and Correll, <sup>17</sup> in a recent discussion of the terminology used in coronary heart disease, cited a case to illustrate "the folly of attaching a clinical label such as 'acute coronary insufficiency' to a phase of a progressive picture which may slowly, rapidly or erratically progress from one end of the spectrum to the other."

Boas <sup>18</sup> studied the clinical course of 124 patients with coronary atherosclerosis for 10 years or longer. He noted that any acceleration of anginal attacks "calls for the presumptive diagnosis of myocardial infarction until it is disproved by the subsequent course of events."

Wolff 19 differentiates between patients with acute coronary insufficiency without demonstrable changes in the myocardium and those with such changes.

Wheeler and Stewart <sup>20</sup> state: "When a constellation of clinical findings appears intermediate between those of angina pectoris and myocardial infarction, it would seem appropriate to use these accepted terms with qualifications rather than to force the diagnosis into some poorly delineated and poorly understood category. Thus, one might diagnose 'severe anginal attack with persistent ischemia not resulting in infarction,' or 'severe anginal attack with questionable infarction of the myocardium,' this latter designation comprising a category into which many cases of so-called 'coronary insufficiency' may readily be listed in our opinion." Unfortunately, busy practitioners will not take the time to use such lengthy terminology.

VanderVeer <sup>21</sup> classified angina pectoris as "chronic" and "acute," probably an unfortunate terminology, since "acute angina" refers to a more active phase of progressive coronary atherosclerosis, usually due to impending or actual myocardial infarction of some degree, or acute coronary insufficiency induced by hemorrhage, excessive physical effort or similar factors.

Physicians need to be cognizant of the wide variability in the clinical manifestations of the syndrome "acute coronary insufficiency." Similar active phases occurring in the course of progressive coronary atherosclerosis are called "coronary failure" by Freedberg and co-workers, 18 but these authors excluded cases with laboratory signs of myocardial necrosis. Others have described patients as having "slight coronary attacks" 22 or "the intermediate coronary syndrome." 23 Such terms denote a physiologic or functional state and do not delineate, except by implication, morphologic changes in the myocardium. Electrocardiographic signs of T flattening or inversion and ST segment depression (or, rarely, elevation) of transitory nature, with or without laboratory evidence of myocardial necrosis and low grade fever, are to some extent common to all of these clinical realms, just as in impending myocardial infarction. The differential diagnosis then depends upon the element of time required for the clinical picture to unfold. If days or weeks pass by and full-blown myocardial infarction does not ensue, then the episode in question is labeled "acute coronary insufficiency." "coronary failure," "intermediate coronary syndrome" or "slight coronary attack," depending upon the favorite terminology of the clinician. Any such classification is made in retrospect only, but should frank infarction develop, the previous clinical state is subsequently acknowledged as the phase of "impending infarction" or the "pre-infarction" stage. In a given case, who can divine at the outset that the initial pain induced by myocardial ischemia is not a harbinger of myocardial infarction?

#### REPORTS OF ANTICOAGULANT THERAPY IN IMPENDING INFARCTION

In 1947 the senior author initiated the use of prompt anticoagulant therapy in the syndrome of "impending myocardial infarction" or "acute coronary insufficiency" in the firm belief that valuable time would be lost if anticoagulants were withheld at the outset until the clinical picture unfolded. Encouraging results were noted in 41 cases.24

In the same year Jaffe 25 suggested the use of anticoagulants in situations where it was impossible to say whether the symptoms were due to acute coronary insufficiency with myocardial necrosis or to the impending stage of myocardial infarction. Wood 26 in 1950 advocated the use of anticoagu-

lants in impending infarction.

Smith and Papp 28 in 1951 described the use of heparin followed by Dicumarol or Tromexan in 14 patients with impending infarction; half of this small group developed infarction, with three deaths. On the other hand, these authors do not advocate anticoagulant therapy in "slight coronary attacks" 22 except when continuation of pain indicates that severe cardiac infarction is impending.29 (We find it difficult to see how patients with "slight attacks" showing only ST segment or T wave electrocardiographic changes could be differentiated at the outset from those with the syndrome of impending infarction.) Further reports in 1952 by Thomp-

son, 30 Maynard 31 and Lenègre and Beaumont 32 indicated beneficial effects of anticoagulants in impending infarction. Additional studies embracing 177 patients were reported by our group in 1954.27 In 1955 Maurice et al.10 reported a study of 71 patients with angina pectoris whose usual pattern of pain had altered, and who were treated with anticoagulants with beneficial effects in all but a few. No clinical criteria could be set up by these authors for determining whether the disease would have progressed to myocardial infarction or not. Engelberg 33 treated 19 patients with impending myocardial infarction with heparin initially, and oral anticoagulants were added after a good response was noted. Engelberg stressed the advantages of heparin over oral anticoagulants. It should be emphasized that the continuous use of anticoagulants prophylactically when myocardial infarction appears imminent is not to be confused with the use of heparin two or three times weekly for its probable effect on blood lipids and angina pectoris, a regimen advocated by Engelberg, as satisfactory proof is lacking that heparin administered in this fashion is of value. 34, 35 Vander Veer 21 advocated heparin and Dicumarol for the pre-infarction anginal syndrome but did not summarize his results. Anderson 36 reserved anticoagulants for those patients not responding to rest, avoidance of trigger factors and use of coronary vasodilators, and of 25 patients treated by him, only one developed acute myocardial infarction. (For the most part, anticoagulants were started in our cases when ordinary therapy had been in force for a long period, except in those patients who for the first time began to exhibit angina pectoris at rest.) Cutts, Merlino and Easton 37 recently selected, in retrospect, 69 patients with angina at rest who exhibited new T inversions in the precordial leads as the only electrocardiographic abnormality. Forty-seven patients received Dicumarol, but only 17 had adequate dosage. No mention was made of early heparinization. These authors state: "Since seven of our patients died within one year after the onset of this syndrome, we are inclined to be less sanguine than some regarding the short term prognosis." With reference to the value of anticoagulant therapy, they added: "However, since only two of our patients died during the original hospitalization and of these one was on adequate Dicumarol therapy, the immediate value of anticoagulants in this type of case remains uncertain. Certainly, this type of therapy does not appear to lessen the hazard of sudden death, nor does it prevent myocardial infarction with any great assurance."

Smith, Keyes and Denham, <sup>38</sup> in reviewing 920 cases of myocardial infarction, noted that 129 (or 15%) had "pilot" anginal attacks varying from a few days to a few weeks prior to the onset of infarction. These authors are currently studying the effect of anticoagulants in the preinfarction state, but point out the difficulty of drawing definite conclusions. <sup>39</sup> Schlachtman <sup>40</sup> reported the failure of heparin given intramuscularly (150 mg. every eight hours) to prevent acute myocardial infarction in three patients who were exhibiting signs of impending infarction. The acute episode developed after

48 hours of therapy in two, and after seven days in the third case. The author stated: "Lee-White coagulation times of 57 minutes have been obtained," but failed to mention how long after a dose of heparin the blood was tested.

# PRESENT STUDY

This study evaluates results obtained in the previously reported series and in 141 subsequent cases comprising 318 private patients who were given anticoagulants during the last 10 years because of signs of impending myocardial infarction. The clinical features of the combined group are shown in table 2. Their ages ranged from 41 to 81 years. There were 71 women and 247 men. Sixty-seven per cent had experienced at least one previous transmural or subendocardial myocardial infarction. In 13 patients it was not possible to be sure whether a previous infarction had taken place. Hypertension was found more than twice as frequently in women (68%) as

Table 2
Clinical Features in 318 Patients with Impending Infarction

Ages	31-40	41-50	51-60	61-70	71-80	Total	
Males Females	5	28 7	89 21	99 26	26 17	247 71	
Total	5	35	110	125	43	318	

Prior myocardial infarction, 216; none, 89; ?, 13. Hypertension in 199, or 37% (males, 32%; females, 68%). Heart failure on occasion, 36%; diabetes, 7.4%.

in men (32%), but diabetes prevailed about equally in both, being found in 26 patients (7.4%). Congestive heart failure was noted on some occasion in 115 patients (or 36%).

### METHODS

As soon as worsening anginal pain occurred, patients were put at rest at home or in hospital, and the usual coronary dilators, tranquilizing agents and sedatives were used. In addition, heparin was begun and continued for from three to 14 days before shifting to oral anticoagulants. The average dosage of concentrated heparin is 75 to 100 mg. every six to eight hours, depending upon the patient's weight and tolerance to heparin as shown by the Lee-White clotting time. Concentrated heparin (100, 200 or 400 mg. per cubic centimeter) is given in the fatty areolar tissue about the iliac crest and abdomen, utilizing a ½ inch, 26-gauge needle. Intramuscular injections are strictly avoided. The clotting times in glass tubes should be carefully performed, as the test is subject to inherent errors, like tests of other clotting factors. The blood should be drawn six to eight hours after a dose of heparin, and the objective is to maintain a clotting time of 25 to 40

Table 3
Anticoagulants and Maintenance Dosage

Anticoagulant	Loading dose,	Maintenance dosage				
Anticoaguant	first 48 hrs.	Range	Usual			
Dicumarol	400- 500 mg.	25-150 mg.	· 75 mg.			
Cumopyran	100- 200 mg.	5- 10 mg.	25 mg.			
Tromexan	1,800-2,400 mg.	150-900 mg.	450 mg.			
Coumadin	50- 100 mg.	6- 25 mg.	40 mg.			
Marcumar	21- 30 mg.	14- 6 mg.	3 mg.			
Sintron	18- 24 mg.	2- 8 mg.	4 mg.			
Hedulin-Danilone	250- 400 mg.	25-200 mg.	100 mg.			
Dipaxin	24- 30 mg.	11- 6 mg.	3 mg.			
Miradon	600- 900 mg.	60-100 mg.	75 mg.			

minutes at the moment of testing, but obviously the clotting time would be longer (over 60 minutes) shortly after a dose of heparin. Table 3 illustrates the various oral anticoagulants used, more than one being utilized in some patients. Methods and precautions in the use of oral anticoagulants have been amply described. The Quick method of prothrombin determination using Simplastin (Warner-Chilcott) was used in all, and in some the Link-Shapiro method was used in addition. Lately the effect of anticoagulants on serum factor VII (proconvertin) has been utilized in adjusting the anticoagulant dosage, and we are currently using another thromboplastin, Acuplastin (Ortho Pharmaceutical Company), which reputedly eliminates the effect of factor VII in the clotting test.

To aid in understanding the vagaries of anticoagulant dosage in longterm cases, studies of other clotting factors, such as the prothrombin consumption time and the thromboplastin generation test, are likewise being conducted.\*

# CLINICAL RESULTS

Relief of anginal pain was usually striking during heparinization. Only 21 of the 318 patients (or 6.6%) developed frank myocardial infarction; 16 recovered, and five died within 30 days. Most of the 21 patients had cardiographic and laboratory changes suggestive of some myocardial necrosis within 24 hours of the time the diagnosis of impending infarction was made.

New electrocardiographic evidence of myocardial ischemia was noted at the outset, or else appeared in a day or so, in 143 additional patients (or 44.9%), including some equivocal cases where modified exercise was used to demonstrate graphic signs of myocardial ischemia. Slight increase in the sedimentation rate of red cells or mild leukocytosis developed in some patients of this group, indicating slight myocardial necrosis. No significant

<sup>\*</sup>Courtesy of Dr. Paul Boyles, Coagulation Research Laboratory, Miami Heart Institute and University of Miami School of Medicine.

alteration in serum transaminase was found since routinely using this test in the last two years except in those patients with frank infarction.

Electrocardiographic or laboratory signs of myocardial ischemia or necrosis failed to develop in 154 patients (or 48.4%).

None of the 297 patients who did not develop frank infarction died while on anticoagulant therapy within a 60-day period. It was our purpose to continue anticoagulants indefinitely in these patients, but 30 stopped the régime within 60 days, an interval we bracket as "short-term" anticoagulant therapy. Of these, 17 (or 56.6%) developed a major "coronary attack" before another 60 days elapsed, only five surviving. This points out the probable correctness of our diagnosis in the group as a whole. One developed new signs of impending infarction and again improved on heparin treatment.

## TABLE 4

Results in 318 Patients with Impending Myocardial Infarction Treated with Anticoagulants, 1947–1957

Frank myocardial infarction developed in 21 (or 6.6%)
Of these, five died within 30 days
New signs of myocardial ischemia appeared in 143 (or 44.9%)
Diagnostic clinical story only in 154 (or 48.4%)
Anticoagulants stopped before 60 days in 30 patients
Of these, 17 (or 56.6%) developed "acute attack" within next 60 days, with 12 deaths

# PERMANENT OR LONG-TERM ANTICOAGULANT THERAPY IN 280 PATIENTS

Two hundred eighty patients, including the 13 survivors of full-blown infarction, continued anticoagulants beyond the 60-day (short-term) period on a permanent basis. The eventual clinical course of the long-term group has been described in part in other papers, <sup>27, 41</sup> and has little bearing on the immediate inquiry as to whether prompt use of anticoagulants actually prevents myocardial infarction in patients suspected of showing prodromal signs. In addition to the 17 deaths mentioned above, 88 patients have died in the intervening years; hence, of the 318 patients, 105 (or 33.0%) are now dead (January, 1958). Congestive heart failure or sudden death, with or without acute myocardial infarction or subendocardial infarction, accounted for all except two noncardiac deaths during the long-term observation period. Renal disease was an added terminal factor in some patients.

Gross hemorrhage, usually mild, never severe or fatal, occurred during the "short-term" therapy in approximately 15% of the cases. Hematuria and hematomas were the most common types of hemorrhage. In no instance was it necessary to use protamine sulfate as a heparin antidote. Water-soluble vitamin K (Hykinone) or, as soon as available, vitamin K<sub>1</sub> (Mephyton)\* was used to counteract drastic hyperprothrombinemia. It

<sup>\*</sup>Early experimental supplies of Mephyton were kindly furnished by Merck, Sharp & Dohme Co.

was necessary to discontinue anticoagulants permanently because of hemorrhage in only two patients.

# DISCUSSION

We did not feel justified in withholding anticoagulant therapy in patients with signs of impending myocardial infarction, hence we present no control group. Many patients displaying premonitory signs never develop infarction even if anticoagulants are not used, especially when activities are restricted, trigger mechanisms are avoided, and appropriate sedatives and coronary dilators are given. The only report available showing what per cent of patients with signs of impending infarction terminate in acute infarction is that of Levy,<sup>42</sup> who found that, of 158 patients with distinct alteration in the pattern of anginal pain, 23.4% developed acute infarction, while in 36% some degree of "moderate myocardial necrosis" took place.

It is not possible to ascertain how many of our patients would have developed full-blown myocardial infarction without heparinization. In the main, it appears that the failure of frank myocardial infarction to develop in more than 21 patients reflects a definite protection afforded by anticoagulants, for it appears highly improbable that clinicians following the customary "watchful waiting" plan of treatment would encounter a consecutive series of 318 patients displaying prodromata of an acute attack with so few eventuating in frank myocardial infarction. A critical survey of our cases not presenting electrocardiographic or clinical evidence of even slight myocardial necrosis might raise the question whether the clinical story had been misinterpreted, and might suggest that no myocardial injury would have ensued in any event, but this is unlikely in view of the natural history of progressive coronary atherosclerosis, an opinion bolstered by the development of a major "coronary attack" within a matter of weeks in more than half of 30 patients who soon abandoned the anticoagulant regimen. Some patients classified as "impending infarction" may well have developed small but unproved infarctions at the outset. Others, particularly those with cardiographic signs of myocardial ischemia persisting for several days, and those developing laboratory evidence of myocardial necrosis, however slight, may be said to have developed some degree of myocardial infarction. In those patients considered to have developed only minor focal necrosis, the signs were not extensive enough to justify the diagnosis of "subendocardial infarction." This is not quibbling, but an honest attempt to identify properly the active phases in the life history of patients with progressive coronary atherosclerosis. It is not practical to look on a patient who has developed one or two isolated clusters of necrotic cells in the myocardium as having myocardial infarction. Just how much disseminated focal necrosis must take place to justify the designation "subendocardial infarction" appears to vary with the clinicopathologic concepts of the clinician. We believe the clinical syndrome under discussion should be

tabbed "impending myocardial infarction" or the "pre-infarction state" as a workable classification. If the clinical concept of the preinfarction state is limited to those patients with a typical story who exhibit new electrocardiographic signs, or only very transitory ST segment and T wave changes without associated leukocytosis or sedimentation rate acceleration, so that heparin is withheld, many lives might be lost, as the extent of myocardial injury appears to be greatly limited by prompt heparinization. Although the prompt use of heparin seems to have greatly limited the development of frank infarction, by the same token it has apparently augmented the number of patients seen with only focal or disseminated necrosis in the myocardium. In recent years, my associates and I find notably fewer frank acute infarction cases on our hands. The friction rub of pericarditis epistenocardiaca has become a collector's item with us!

Even if we drop from consideration the 143 patients who showed new cardiographic signs of protracted myocardial ischemia and slight elevation in the leukocyte count or sedimentation rate, and classify them as having developed a sufficient degree of subendocardial necrosis to warrant the diagnosis of "infarction," many of the 154 patients who did not show these signs may well have been prevented from even minor myocardial necrosis or infarction by the prompt use of heparin at the onset of the altered pain pattern. In the treatment of impending infarction the dictum of LeRoy and Snider <sup>43</sup> anent their study of sudden cardiac death in the absence of striking symptoms seems apropos: "Suspicion rather than certainty should determine the physician's conduct."

#### SUMMARY

The various syndromes due to coronary atherosclerosis and the difficulties encountered in pinpointing the exact phase of coronary atherosclerosis that a patient is manifesting have been outlined. The need for careful classification of the "active phases" punctuating the life history of patients with progressive coronary atherosclerosis has been emphasized. The distinction, except in retrospect, between the syndrome of "acute coronary insufficiency," "coronary failure," "intermediate coronary syndrome," "slight coronary attack" and "impending myocardial infarction or the pre-infarction syndrome" is wholly artificial. Only time certifies the diagnosis, which cannot be made by the laying on of hands.

Three hundred eighteen consecutive patients with acceptable criteria of impending myocardial infarction encountered by the authors in private practice were treated promptly with heparin and later on with oral anticoagulants. Two hundred sixteen patients had experienced one or more previous attacks of myocardial infarction, while 89 had never suffered an attack, and in 13 it was impossible to determine whether previous attacks had taken place. New electrocardiographic or clinical signs of myocardial ischemia or focal myocardial necrosis were either present initially or de-

veloped later in 143 patients (or 44.9%). The diagnosis was based solely on the patient's story in 154 (or 48.4%).

Only 6.6% developed frank myocardial infarction, five of whom died within a month. None of the others died while using anticoagulants within 60 days of observation. Of 30 patients abandoning anticoagulants before 60 days, 17 (or 56.6%) developed "an acute coronary attack" within the next 60 days, with 12 deaths in the following two months. Two hundred eighty patients were sustained on long-term anticoagulant therapy indefinitely, and in the intervening years 88 more patients died, mainly of cardiovascular disease, many having abandoned the anticoagulant regimen.

Comparable controls are not provided in this study, but the prophylactic benefit of prompt heparin therapy followed by oral anticoagulant therapy in patients showing signs of threatened myocardial infarction appears to be clearly demonstrated. The relief of anginal pain with heparin was often striking.

#### ADDENDUM

The following concepts of the various clinical-pathologic phases of progressive coronary atherosclerosis are suggested. It would be fruitful if the American Heart Association would set up a committee on clinical nosology to standardize acceptable terminology.

1. Angina pectoris: pain of brief duration due to myocardial ischemia *not* associated with laboratory evidence of tissue destruction.

2. Acute transmural or subendocardial myocardial infarction, with or without coronary occlusion (frank, mild or minor).

3. Impending infarction or pre-infarctional state: when angina pectoris is worsened or protracted, or changes its character spontaneously with atypical benefit of nitroglycerine. Only time determines whether tissue necrosis, even minimal, has developed and, if so, then a minor or major infarction, with or without acute coronary occlusion, has taken place, and such a pathologic diagnosis is made in retrospect.

4. "Acute coronary insufficiency," "coronary failure" and "intermediate coronary syndrome" are terms which should be applied only in retrospect to those situations where a provocative factor, such as hemorrhage or shock, has induced prolonged reduction in coronary flow and protracted myocardial ischemia, usually with some degree of myocardial necrosis.

#### ACKNOWLEDGMENT

We wish to thank Mrs. K. Ellison, R.N., for her help in compiling the clinical data.

#### SUMMARIO IN INTERLINGUA

Le syndrome de imminente o menaciante infarcimento myocardial non pote esser distinguite *initialmente* ab le syndrome de "acute insufficientia coronari" de origine spontanee. In 1947 le autor senior initiava le uso de prompte therapia anticoagulante in patientes qui pareva exhibir signos de menaciante infarcimento myocardial

o de "acute insufficientia coronari." In le curso del passate 10 annos nos ha tractate 318 patientes consecutive qui exhibiva signos premonitori de infarcimento myocardial. Le serie includeva 247 masculos e 71 femininas de etates de inter 41 e 81 annos. Sexanta-septe pro cento del patientes habeva habite al minus un previe infarcimento myocardial. Heparina de forma concentrate esseva usate per via subcutanee a intervallos de sex horas durante periodos de inter tres e 14 dies, sequite per varie anticoagulantes oral. Restriction de activitate physic esseva imponite, e agentes vasodilatatori e sedative esseva utilisate.

Resultatos: Solmente 6,6% del patientes disveloppava franc infarcimento myo-

cardial. Occurreva cinque mortes.

Nove testimonio electrocardiographic de ischemia myocardial esseva notate precocemente in 143 patientes (44,9%), incluse un numero de casos equivoc in que exercitios modificate esseva utilisate pro demonstrar signos graphic de ischemia myocardial. Un leve acceleration del sedimentation erythrocytic o leve grados de leucocytosis esseva constatate in plure membros del gruppo.

Nulle signos electrocardiographic o laboratorial de ischemia myocardial o de

necrosis in le myocardio esseva manifeste in 154 patientes (48,4%).

Nulle del 297 patientes le quales escappava al disveloppamento de franc infarcimento myocardial durante lor curso de therapia anticoagulante moriva intra un periodo de 60 dies. Trenta interrumpeva le uso de anticoagulantes post minus que 60 dies. De istes, 12 (i.e. 56,6%) disveloppava un major "attacco coronari" ante le fin de 60 dies additional. Solmente cinque del del 12 superviveva. Isto indica con alte grado de probabilitate que nostre diagnoses in le gruppo total esseva correcte. Hemorrhagias occurreva in 15% del casos. Nulle esseva mortal.

Duo centos octanta patientes, incluse 13 superviventes de franc infarcimentos, continuava le uso de anticoagulantes a base permanente. Lor destino a longe vista es describite alterubi. Octanta-octo patientes ha morite in le curso del annos interveniente. Assi, 105 (i.e. 33,0%) del 318 patientes es morte. Le causa de morte in

omne le casos-con duo exceptiones-esseva de natura cardiac.

Nos non nos credeva justificate a denegar le therapia anticoagulante a patientes con signos de imminente infarcimento myocardial. Per consequente il non es possibile assèrer in quante casos franc infarctos myocardial se haberea disveloppate sin le uso de heparina. Il es probabile que le non-occurrentia de franc infarcimento myocardial reflecte in le majoritate del casos un definite effecto protectori exercite

per le anticoagulantes.

Le grado de disseminate necrose focal que debe occurrer pro justificar le designation "infarcimento subendocardial" varia apparentemente con le conceptiones clinicopathologic del clinicos individual. Si le concepto clinic de "stato pre-infarcimental" es restringite de maniera a devenir applicabile solmente a patientes con un historia typic qui exhibi nulle nove signos electrocardiographic o solmente alterationes transitori del segmento ST o del unda T-sin associate leucocytosis o accelerate sedimentation erythrocytic-e si alora, in consequentia de un tal definition, heparina es denegate al altere patientes, il es probabile que le resultato es le perdita de numerose vitas, proque il pare que le grado del lesiones myocardial es grandemente restringite per le prompte uso de heparinisation.

Mesmo si nos lassa foras de consideration le 143 patientes qui exhibiva nove signos cardiographic de prolongate ischemia myocardial e leve augmentos del numeration leucocytic o leve accelerationes del sedimentation erythrocytic e classifica les como habente disveloppate un grado sufficiente de necrose subendocardial pro justificar le diagnose de "infarcimento," multes del 154 patientes qui non monstrava ille signos esseva salvate—con alte grados de probabilitate—ab le occurrentia de al minus minor formas de necrose o infarcimento myocardial per le prompte uso de heparina al

momento quando un alterate configuration de dolores se declarava.

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# DERMATOMYOSITIS AND MALIGNANCY: A REVIEW OF THE LITERATURE\*

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SINCE the original descriptions by Wagner <sup>1</sup> and Unverricht <sup>2</sup> in 1887, dermatomyositis has become a well recognized clinical and pathologic entity. Whether the symptom complex which presents itself as dermatomyositis is truly one disease is open to question, particularly in view of the incidence of associated malignancy in the cases reported. In 1916 Stertz <sup>8</sup> first called attention to dermatomyositis coupled with neoplasm in a 55 year old man with carcinoma of the stomach who presented with polymyositis. Bezecny <sup>4</sup> in 1935 refocused attention upon the association of tumor and dermatomyositis in his report of three cases, two with ovarian neoplasm and one with carcinoma of the breast. In a review of 344 cases reported between 1916 and 1950 Schuermann <sup>5</sup> noted 45 instances (13%) of associated malignancy. The more recent reports of Curtis et al., <sup>6</sup> Sheard, <sup>7,8</sup> Caldwell <sup>9</sup> and Dowling <sup>10</sup> have stressed the association between dermatomyositis and cancer.

Of the 590 cases in the literature, 92 reported tumor accompanying dermatomyositis. In many instances only brief mention was made of such patients, but wherever details were available an analysis of the clinical course of the dermatomyositis was made, with particular emphasis on the available pathologic data.

Among the 92 case reports there was an almost equal distribution of the sexes, 47% being females and 53% males. As can be seen from figure 1, the majority of patients were between the ages of 40 and 70. Sites most frequently involved by malignancy were as follows:

- 1. Stomach, 16 cases. 3, 5, 8, 17, 22, 29, 30, 34, 37, 44, 48, 49, 52, 54
- 2. Breast, 15 cases. 4, 6, 8, 11, 18, 17, 20, 25, 32, 38, 38, 40, 46
- 3. Lung, 14 cases. 7, 9, 10, 26, 28, 86, 42, 48, 47, 51
- 4. Ovary, 10 cases. 4, 7, 8, 10, 16, 25, 81, 86, 55
- 5. Lymphoma and leukemia, nine cases. 5, 6, 19, 21, 22, 45, 50
- 6. Gall-bladder, four cases.7, 12, 18, 41
- 7. Colon and rectum, four cases. 8, 28, 80
- 8. Kidney, three cases. 26, 85, 87
- 9. Uterus, three cases. 18, 89, 58
- 10. Larynx, three cases. 22, 89, 51

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Less frequent tumor origins included: multiple myeloma, retroperitoneal sarcoma, parotid carcinoma, endothelial sarcoma, carcinoma of cervix, epithelioma of vagina, carcinoma of esophagus, plasmacytoma, chromophobe adenoma and substernal sarcoma.<sup>6, 14, 15, 17, 24, 27, 34</sup> Striking by their absence were carcinoma of the prostate and carcinoma of the pancreas, important causes of death by cancer in the age group studied.

In the review of the case reports of dermatomyositis coupled with malignancy it became apparent that those patients with neoplasm accompanying, preceding or following the onset of their dermatomyositis fell into a clinical picture more sharply defined than is the general clinical spectrum of patients with dermatomyositis alone. Particularly striking was the acute onset of symptoms: usually rash occurring on those parts of the body most often exposed to the sun, e.g., face, dorsum of hands, arms, neck and thorax. In 20 of 58 cases where full histories were available, skin rash preceded muscu-

#### DISTRIBUTION OF TUMOR SITES IN PATIENTS WITH DERMATOMYOSITIS

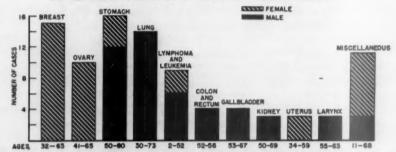


Fig. 1. Distribution of tumor sites in patients with dermatomyositis.

lar symptoms of pain, weakness or loss of substance. The sites of initial skin lesions are noted in table 1. The character of the skin lesions varied from edema and mild erythema to florid, blue-red, mottled, purpuric eruptions with desquamation and intense pruritus. In many patients a history of previous exposure to the sun was noted, and the skin manifestations were thus misinterpreted initially as being those of disseminated lupus erythematosus.

Muscular symptoms and signs in patients with dermatomyositis and malignancy did not differ from those in patients with dermatomyositis alone. Degree of eosinophilia, electrical reaction of muscles to galvanic and faradic current, creatinuria and creatin tolerance were similar in patients with dermatomyositis alone and in those with neoplasm and dermatomyositis.

Among 58 reports in which details were available, 47 patients had dermatomyositis which preceded clinical or pathologic recognition of associated tumor, whereas 11 developed dermatomyositis after tumor had been discovered. In the latter group, tumor had preceded dermatomyositis by

TABLE 1

1. Site of initial skin rash in 58 patients where details were available

Face	47 patients
Neck	30 patients
Arms	41 patients
Hands	18 patients
Chest	16 patients
Legs	5 patients

2. Time at which muscle complaints became manifest (54 patients)

Onset of Illness at Time of Rash	Before Rash	After Onset of Initial Skin Rash
32 patients	1 patient	21 patients

Time at which dermatomyositis made its appearance in relation to tumor (58 patients reported in whom this could be determined)

Dermatomyositis Preceding Tumor, Later Found in Clinical Course or at Autopsy	Dermatomyositis Following Recognition of Tumor
47 patients	11 patients

 Effect on dermatomyositis of therapy directed against coexisting tumor (only nine patients found in whom this could be judged)

Site of Tumor	Therapy	Effect on Dermatomyositis
1. Ovary	Surgery	Facial edema and rash decreased
2. Ovary	X-ray	Improvement in muscle weakness and skin lesions
3. Ovary	Surgery	Marked improvement in both skin and muscle complaints
4. Breast	Surgery	Improvement in muscle weakness
5. Breast	Surgery	Skin rash showed slight regression
6. Breast	Surgery and x-ray	Improvement in both muscle and skin complaints
7. Stomach	Palliative surgery	Slight improvement in muscle weakness
8. Uterus	X-ray	Improvement of both skin and muscle complaints
9. Vagina	X-ray	Slight improvement of muscle weakness

intervals of from seven years to several weeks. There was no correlation between intensity of the dermatomyositis and evidence of widespread disease. Among the 58 cases reported in detail, 15 patients (26%) showed no gross evidence of metastatic disease from their tumors at autopsy.

Improvement in dermatomyositis after treatment for associated malignancy was first described by Bezecny.<sup>4</sup> In the cases reviewed, amelioration of symptoms was most often noted after treatment (surgical, x-ray or hormonal) for carcinoma of the ovaries and breast, though a single instance of amelioration of skin rash and muscle complaints was reported after gastrectomy for carcinoma of the stomach. The effect of tumor therapy upon dermatomyositis remains obscure in the majority of cases reviewed, either because no tumor was suspected before death, or because effective treatment was not available.

# Discussion

It is interesting that a disorder which has been placed in the "collagen disease" group should have a significant association with malignancy. In 590 cases published to date, tumor has been present in 92 patients (15.3%).

This figure may be artificially high, since reports of such associations would be more likely to find their way into the literature than would those of dermatomyositis alone; however, the possibility that cancer associated with dermatomyositis is a chance connection seems unlikely. Sheard <sup>8</sup> found only one case with "incidental" malignancy in 50 patients dying of myocardial infarction in an age group comparable to those he studied with dermatomyositis. Moreover, the sometimes dramatic improvement in dermatomyositis after antitumor therapy lends weight to the concept that the two conditions are in some way related.

Numerous echoes of similar companions to malignancy have received attention in the literature. Migratory thrombophlebitis with visceral cancer and hypertrophic pulmonary osteoarthropathy with intrathoracic tumor are well recognized examples. Among the skin disorders, acanthosis nigricans and recurrent herpes zoster have often been harbingers of neoplasm. Ichthyosiform atrophy of the skin has been noted in Hodgkin's disease. 56 Greenfield 57 mentioned a peculiar group of spinocerebellar degenerations in which patients with malignancy showed loss of cells in cerebellum and long tracts without evidence of metastatic disease to the central nervous system. It is pertinent to note that in Greenfield's group of 14 patients, seven had ovarian carcinoma, three carcinoma of the uterus, two carcinoma of the breast, and two bronchogenic carcinoma. Denny-Brown 58 noted an unusual form of peripheral neuropathy in two patients with bronchogenic carcinoma. Pathologic degeneration was striking in dorsal root ganglia and in the dorsal columns of the spinal cord. Both of these patients exhibited microscopic evidence of polymyositis, though muscular complaints were not prominent during their illnesses. Another peculiar companion to malignancy is found in the association of renal tumors 59 and certain brain tumors 60 with polycythemia. Amyloidosis of the secondary type has often been noted with carcinomas in various sites. 61 A final interesting association is that of mongolism with leukemia, where mongols show three times the expected incidence of leukemia in the "normal" population. From such associations it may be possible in the future to study segments of tumor metabolism in an isolated fashion.

Speculation as to whether underlying malignancy can start a dermatomyositis-like disease process is appealing. From the cases so far reported it seems likely that in many instances the associated neoplasms have at least coincided with the clinical development of dermatomyositis. It would be injudicious to interpret what may be merely guilt by association as a cause-and-effect relationship, but the possibility that tumor products cause dermatomyositis remains. The explanation might be advanced that the skin and muscle were participating in a natural defense reaction to blood-borne carcinoma cells or cell products. However, the absence of notable incidence of skin or local soft tissue metastatic disease in the reported case detracts from this explanation.

Endocrine imbalance is an attractive hypothesis to explain dermatomyositis and associated malignancy, particularly when one notes the high incidence of breast and ovarian tumors so far reported. O'Leary and Waisman's careful study of 40 cases of dermatomyositis seen at the Mayo Clinic 28 mentions two patients with features of Cushing's syndrome. Certainly the muscular weakness, creatinuria and microscopic picture in the affected muscles of Cushing's syndrome can mimic dermatomyositis. Sunde 27 reports a case of dermatomyositis in an 11 year old child who was later found to have a chromophobe adenoma—present in retrospect at the time of her initial dermatomyositis. One of the patients seen at The New York Hospital (previously reported by Sheard 8) was found to have metastatic tumor in the pituitary gland which was removed for treatment of her metastatic carcinoma of the breast. For four months after hypophysectomy there was a striking regression in complaints referable to her associated dermatomyositis before metastatic disease caused her deterioration.

Whatever the exact relationship between malignancy and dermatomyositis, cause-and-effect, or merely partners in evil, the symptom complex of acute onset with predominant skin involvement of face, hands, arms and neck in a patient of middle age should make the clinician undertake a careful search for occult tumor.

#### SUMMARY

1. Ninety-two cases of dermatomyositis associated with malignancy are reviewed, with emphasis on the similarities of their clinical pictures.

2. Acute onset of skin rash and muscle complaints progressing to dermatomyositis in a patient of middle age may presage malignancy.

3. Most common sites for associated neoplasms were: stomach, breast, ovaries, lung, reticuloendothelial system, gall-bladder, colon and rectum, and kidney, in that order.

4. The incidence of malignancy in dermatomyositis cases reported to date is 15%.

5. Therapy directed at associated neoplasm may provide a dramatic temporary remission in dermatomyositis.

#### ADDENDUM

Since this article was originally prepared, 12 other case summaries have appeared in the literature 68-71 which reveal the association between dermatomyositis and malignancy. Previously unreported primary sites of tumor include carcinoma of the pancreas; 94 however, the other primary sites—gall-bladder, breast, ovaries, cervix; and the association with lymphoma—had been covered in the earlier reports.

# SUMMARIO IN INTERLINGUA

Le prime reporto de dermatomyositis associate con malignitate esseva facite per Stertz in 1916.<sup>3</sup> Subsequentemente le phenomeno ha recipite crescente grados de attention in le litteratura, <sup>4, 5, 6, 7, 8, 9, 10</sup> Inter 590 casos de dermatomyositis reportate in le litteratura, 92 esseva associate con tumores. In le correspondente 92 reportos,

le representation del duo sexos esseva quasi identic. Le etates del patientes variava inter 40 e 70 annos. Le plus commun sitos del associate malignitate esseva le stomacho (16 casos), le pectore (15 casos), le pulmon (14 casos), le ovarios (10 casos), le vesica biliari (4 casos), le colon e le recto (4 casos), le ren (3 casos), le utero (3 casos), e le larynge (3 casos). Le serie etiam includeva sex casos de lymphoma e nove casos de leucemia. Minus frequente esseva le casos de multiple myeloma, sarcoma retroperitonee, carcinoma parotidic, sarcoma endothelial, carcinoma del cervice, epithelioma vaginal, carcinoma del esophago, plasmocytoma, adenoma chromophobe, e sarcoma substernal. Un facto frappante esseva le absentia de carcinoma del prostata e de carcinoma del pancreas.

Le tableau clinic del patientes con dermatomyositis e malignitate esseva characterisate per un declaration acute del symptomas, frequentemente con manifestationes cutanee ante que symptomas muscular esseva presente. Ex un serie de 58 reportos complete, 47 concerneva patientes in qui dermatomyositis precedeva le recognition del associate tumores. In le altere 11 casos, dermatomyositis es disveloppava post que le tumor habeva essite determinate. Melioration de dermatomyositis esseva notate le plus frequentemente post cursos de tractamento pro carcinoma de ovario o pectore.

Le incidentia de tumores occurrente in association con dermatomyositis es 15,3% super le base del disponibile reportos. Simile associationes con morbo maligne es a notar in thrombophlebitis migratori, osteoarthropathia pulmonar, acanthosis nigricante, e recurrente herpete zona. Degeneration spinocerebellar, neuropathia peripheric, polycythemia, e amyloidosis se trova etiam como companiones de malignitate.

Es presentate speculationes con respecto al question de causa e effecto in iste situation. Le alterationes cutanee e muscular de dermatomyositis es possibilemente reactiones al presentia de cellulas maligne o forsan reflexiones de un imbalancia endocrin.

Le complexo de symptomas characterisante le declaration de dermatomyositis in un patiente de etate medie deberea esser reguardate como un indication pro le plus meticulose cerca de un tumor occulte.

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# POLYCYTHEMIA VERA. I. CLINICAL AND LABORATORY MANIFESTATIONS \*

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Originally described by Vaquez in 1892, polycythemia vera was established as a definite clinical entity by the subsequent reports of Saundby and Russell 2 and Osler 3, 4 at the turn of the century. The early historical and investigative accounts of this condition have been thoroughly reviewed in the literature.5,6,7

By 1940 two distinct contributions had been made which laid the foundation for our present-day concepts of the nature and therapy of the disease: (1) the description of the various clinical stages of the disease by Rosenthal and Bassen,8 and (2) the introduction of radioactive phosphorus by Lawrence. Notwithstanding these advances, polycythemia vera was still considered to be an uncommon disease at that time. 10 According to Dameshek and Henstell,10 lack of recognition of the clinical picture was, at least in some part, responsible for this.

Subsequent interest, spurred by the encouraging results and increased availability of radioactive phosphorus, resulted in several reports of sizable series of cases. 11, 12, 18, 14, 15 Although in most instances the authors included a description of the clinical manifestations of the disease, attention was primarily focused on the technical aspects and therapeutic effects of the new drug. A series of 125 cases collected in several clinics in Denmark and all treated with methods other than P82 was reported by Videbaek.16

More recently, comprehensive reviews 17, 18 regarding the pathogenesis, course and therapy of polycythemia vera have been published. One of these 18 deals at some length with the clinical description of the cases.

It is the purpose of our papers to report the experience of the University Hospitals with this disease since the advent of P32 therapy. In this section we will deal with the clinical and laboratory manifestations at the time of diagnosis, in an effort to focus the attention of the clinician upon the early recognition of this condition.

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## CASE MATERIAL

Radioactive phosphorus has been used in this clinic since 1946, when it became generally available. Since that time, 107 cases diagnosed as polycythemia vera have been treated with one or more doses. At the time of this study, five of the hospital charts were not available. Two additional cases have been omitted. One was a 50 year old white male who died one year after diagnosis and at autopsy was found to have an extensive pulmonary fibrosis probably related to a pneumoconiosis of unknown etiology. It was the opinion of the pathologist that the polycythemia was probably secondary to the pulmonary disease. The other case which was not included was that of a 42 year old male who complained of nervousness. He had but slight elevation of his red cell count and hemoglobin, no palpable liver or spleen, and was primarily a psychiatric problem. His subsequent course favored the diagnosis of "stress" polycythemia.

Generally speaking, there is no single symptom, sign or laboratory test that is pathognomonic of polycythemia vera; rather, a composite clinical picture is what the diagnosis should be based upon. 10, 18, 22 All of our cases were clinically diagnosed, and the diagnosis was critically reviewed from the hospital charts. We relied mostly upon persistently elevated erythrocyte counts and hemoglobin in the absence of obvious cause. Hepatomegaly, splenomegaly, plethoric appearance, elevated platelet and leukocyte counts, and appropriate symptomatology, when present, served as strongly supporting evidence.

Age at Diagnosis: The age distribution at time of diagnosis is indicated in figure 1. Our patients ranged from 24 to 79 years of age, with an average age of 54 years (52 for males and 58.5 for females). Other investigators have reported similar findings. <sup>16, 17, 18</sup> It is important, however, to realize that this merely represents the age at which the process is recognized, not the age of onset. It is generally accepted that there is a developmental stage when the patient is either asymptomatic or has symptoms which are not severe enough to elicit a diagnosis. This may be because the patient does not seek a physician or, with the present-day practice of routine physical examinations, it is not unlikely that an appreciable number of cases are not recognized by the doctor in the early phase.

Although it has been estimated that this prediagnosis period is about five years in length, 28 accurate figures are not available. A review of the histories and referral letters of our patients showed that definite symptoms related to polycythemia were present, on the average, two years prior to diagnosis. Fifteen patients complained of symptoms related to their present illness for more than five years. We have no way of determining for how long any of these patients had elevated erythrocyte counts before symptoms developed.

Sex, Race and Religion: Sixty-four patients in our group were males and 36 were females. This male-to-female ratio of 1.8 is in agreement with

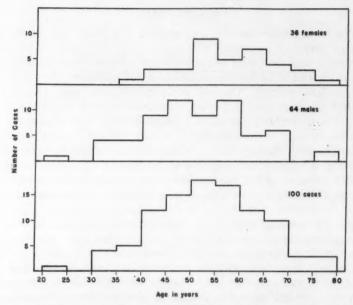


Fig. 1. Age distribution at time of diagnosis of polycythemia vera for the entire group and for each sex separately.

that reported in the literature.<sup>11, 16, 17, 18</sup> The male preponderance and the higher incidence of the disease in women over 50 years of age, with a later average age in our series, offer grounds for conjecture on possible endocrine-regulatory mechanisms. Much has been written about possible hormonal influences on red cell production and its significance in the etiology of this disease, <sup>36, 36, 37, 38</sup> but this is beyond the scope of this article.

All of our patients were white, and only three of them were Jewish. Earlier authors stressed the predominance of the condition among Jews born in eastern Europe. 10, 24 However, more recently, reports of large series without any Jews 16 or with no particular ethnic group preponderance 18 have appeared. Our data show no significant deviation from the general ethnic distribution in this hospital.

Familial Incidence and Occupation: The occurrence of polycythemia or leukemia in close relatives of patients with polycythemia vera has not been frequently reported. Spodaro and Forkner 32 critically reviewed the literature in 1933 and accepted only six authenticated cases of familial polycythemia. They also described in the same article a family in which seven of 10 members had polycythemia, four with splenomegaly and three without. An additional sibling had splenomegaly without polycythemia. However, because of the absence of leukocytosis, the normal hemoglobin values, and normal basal metabolic rates, they preferred to classify this as a separate

entity, and suggested the term "benign familial polycythemia." Nadler and Cohn <sup>33</sup> argued against this differentiation on the grounds that, with the elevation of the red cell mass present, it was justifiable to include the group of cases with those of polycythemia vera. In addition, they reported another family in which four of 11 children had polycythemia. Only one child had a palpable spleen, but all had an increase in blood volume.

Lawrence and Goetsch <sup>34</sup> in 1950 added one more family in which two cases of polycythemia and one of myelogenous leukemia were present among three siblings. In a later publication from the same clinic, <sup>18</sup> probably the same family, with an additional case in a niece, is mentioned, as well as still another family instance in the father of a different patient.

There have apparently been even fewer cases of leukemia and polycythemia within the same family. To the four reported in the literature up to 1950, Lawrence and his group have added four more.<sup>18, 34</sup>

In view of the reported infrequency of these occurrences, we analyzed the charts of our cases for these associations. It should be emphasized that we have not personally studied the relatives of these cases, and the information reported was obtained from the family history given by the patient.

Two patients reported having a close relative with leukemia. One of these stated that an uncle also had a condition similar to her own disease. A 45 year old man has a documented positive history for polycythemia vera in two other members of his family, a brother and a sister. In addition, two other brothers, and a son of one of these, have splenomegaly without polycythemia. Three other sisters are said to have no positive findings.

Four other patients have relatives in whom they describe a picture which seems to be that of polycythemia. One of these has a sister with pernicious anemia. An interesting occurrence which may be mentioned here is that a married couple with polycythemia vera is included in our series. There does not seem to be a previous history of the disease in either family. Two sons, 41 and 43 years of age, have hematocrits of 53% and erythrocyte counts of 5.5 and 6.4 million without symptoms or splenomegaly. A daughter has not been seen in our clinic but is said to have a normal blood count. One other child died of pneumonia. No toxic or other environmental factor has been recognized.

There appears to be no particular occupational risk connected with polycythemia vera in our series. The high incidence of farmers and housewives is consistent with the general population in the state.

# PRESENTING SYMPTOM (CHIEF COMPLAINT)

A very important clue to the nature of a patient's illness is often obtained early in the course of a medical history from the patient's "chief complaint." This may be second in importance only to the general appearance of the patient on first contact in opening certain avenues of thought in the mind of

the interviewer. Although it is an integral part of the history-taking routine of most physicians, it has been hitherto neglected in polycythemia vera.

In table 1 we have listed in decreasing order of frequency the chief complaints at the time of the original diagnosis in the present series of cases. When more than one symptom brought the patient to medical attention, each is listed separately. This situation was present in 12 of our cases. When the presenting complaint or complaints were established to be the results of a thrombotic episode, they were listed only under thrombotic manifestations and not under extremities, chest pain, syncope, etc.

Table 1
Presenting Symptoms (Chief Complaint) in 100 Cases of Polycythemia Vera

Symptoms	Total Number	Males	Females	
Weakness	15	12	3	
Abdominal pain	14	10	4	
Incidental	11	9	2	
Routine physical examination	5	4	1	
Upper respiratory infection	2	2	0	
Benign prostatic hypertrophy	2	2	-	
Orthopedic disorders .	2	1	1	
I hrombotic manifestations	10	8	2	
Extremities	7	6	1	
Coronary	1	1	0	
Cerebral	2	1	1	
Vertigo	10	9	1	
Erythema	9	3	6	
Headache	8	5	3	
Syncope	5	4	1	
Disturbances of the extremities	5	4	1	
Psychiatric manifestations	3	1	4	
Chest pain	4	3	1	
Dyspnea	4	3	1 4	
Visual complaints Paresthesias	4 .	2	2	
Pruritus	2	1	2	
Bleeding tendencies	3	2	1	
Abdominal tumor	2	ő	2	
High blood pressure	2	1	1	
Renal symptoms	2	1	1	
Constipation	2	Ô	2	
Hot spells	i	0	1	

Under the category "incidental" we have listed all individuals in whom the diagnosis of polycythemia vera was made while the patient was undergoing an examination for symptoms of a condition clearly unrelated to their hematologic disturbance or during a general check-up. On further questioning, all but three of these patients complained of symptoms which could be considered secondary to their polycythemia, but had not been severe enough to cause them to seek a physician. Therefore, in only three instances was the disease really discovered in the "asymptomatic stage."

It is of interest that, following weakness and abdominal pain, which were the two most common presenting symptoms, incidental discovery of the disease was responsible for recognition of more cases than other classic manifestations such as thromboses, vertigo, erythema and headache. No striking differences in symptomatology for different age groups were found.

# GENERAL SYMPTOMS

Table 2 lists for comparison the symptoms present in our cases and those found by five other clinics in this country. 10, 11, 18, 15, 18 The composite sums of cases which presented a particular symptom appear in the extreme right hand column, with the appropriate percentage of occurrence. The symptoms are arranged in descending order of frequency as obtained from these totals. Although 541 cases in total are represented from these six institutions, it was not possible in every case to match the data presented by other authors to our particular subdivisions. A blank was left when we were unable to find the particular symptom listed. Two series 10, 18 included summaries of additional symptoms present in the patients besides the tabulated incidences of the more common ones. We reviewed the information given, and whenever possible, included it in our table with an asterisk beside it to indicate that these figures were not compiled by the respective authors. They are probably not entirely accurate.

In some instances the indefinite nature of a particular symptom was the reason why some authors did not include it in their tabulation. For example, Lawrence 18 states that fatigue of some degree was a very common

TABLE 2 Symptoms in Polycythemia Vera

	Clinic Reporting and Number of Cases									Total No.				
Symptoms	U. of Cal. Berkeley <sup>18</sup> 159		Mayo Cl. Rochester <sup>11</sup> 124		Ohio St. U. Columbus <sup>15</sup> 108		Wash, Univ. St. Louis <sup>13</sup> 30		Beth Israel Hospital Boston <sup>10</sup> 20		University Hospital Madison 100		of Cases and % 541	
Weakness and fatigue Headache Dizziness and vertigo	72 45	‡ 45% 28%	82 71 65	66% 57% 52%	51 34 43	47% 31% 40%	34 22 15	31% 73% 50%	8 18 14	40% 90% 70%	49 59 54	49% 59% 54%	210 276 236	55% 51% 44%
Disturbances of the extremities Psychiatric	-	-	-	-	-	-	14	47%	7	35%	44	44%	65	43%
manifestations Dyspnea and orthopnea	54	34%	_	_				/0	7*	35%	46	46%	107	42% 35%
Constipation Bleeding tendencies	-	•	41	33%		_	-	-	14	70%	27 30	30%	41 79	34%
Visual complaints Paresthesias Abdominal pain	43	27%	40 33	32% 27%	=	_	11 4* 7*	37% 13% 23%	6 12 10	30% 60% 50%	34 36 36	34% 36% 36%	134 85 93	31% 31% 30%
Thrombotic manifestations Pruritus	49	31% 14%	34 41	27% 33%	24† 24	17%	6*	20% 50%	9 2*	45% 10%	20 20	20%	142 124	26% 23%
Weight loss Chest pain	25	16%	_	=	_	-	3*	10%	5*	25%	20 17	20% 17%	20 50	20% 16%
External ocular disturbances Syncope		_	_	_		=	5	17%	2 2*	10% 10%	16 8	16%	23 11	15%

<sup>\*</sup> Compiled from case summaries included in report.

<sup>†</sup> Total of 138 cases studied for this complication.

<sup>1</sup> Mentioned as common but hard to evaluate.

<sup>§ 10%—</sup>probably only severe manifestations reported (see text).

finding, but it was not listed because of the obvious difficulty in evaluating such a symptom. This was undoubtedly the case with other findings, particularly psychiatric disturbances, constipation and weight loss. We concur with these writers in their opinions, and submit that our figures should be interpreted with the full understanding of their inherent limitation.

There was general agreement among all the investigators that weakness and/or fatigue and headache constitute the most common symptoms, each occurring in slightly over half of the cases studied. As previously noted, weakness was also the most common chief complaint. These were followed by symptomatic manifestations in the extremities, dizziness or vertigo, and psychiatric disturbances.

Some confusion may arise as to interpretation of complaints referable to the extremities. For example, some writers prefer to list separately the incidence for thrombophlebitis, arthritic complaints or bone pain. Admitting that this is an arbitrary matter, we chose to include under our grouping "extremities," any manifestation of pain, severe swelling and ulcerations occurring in the arms or legs. Whenever definite thrombophlebitis was present, it was listed only under thrombotic manifestations. In three other large series 11, 15, 18 this particular subdivision was not adopted.

Psychiatric manifestations, grouped as such, were not listed by other authors. The difficulty in interpreting this category has been mentioned. We believe, however, that because of its high frequency it should be included, if only as an approximation. It should be emphasized that in evaluating this complaint we accepted its presence only when a persistent and severe degree of nervousness, anxiety or altered mental state of recent onset existed. In most cases this was evaluated by a neuropsychiatric consultant, and disappeared following therapy for the polycythemia. It is widely accepted that reversible psychiatric disturbances of more or less marked severity are present in this disorder, and approximate data derived from case summaries published by other investigators 10, 13 confirm their relatively high frequency.

The next group of symptoms, occurring in approximately one third of the cases reviewed, includes: respiratory complaints (dyspnea and orthopnea), bleeding tendency, constipation, visual disturbances, paresthesias and abdominal pain.

That respiratory distress occurs in slightly over one third of patients with polycythemia vera is of obvious clinical importance. The physician's first problem in evaluating this type of disorder is to differentiate it from the secondary polycythemias which occur in cardiorespiratory diseases. A normal or slightly reduced arterial O<sub>2</sub> saturation is usually helpful in this differentiation. The diagnosis of polycythemia vera should not be discarded because of the presence of even severe respiratory distress. The explanation for this appreciable incidence of dyspnea probably lies in a combination of mechanical factors. The frequently advanced age of the

patient, with its concurrent pulmonary changes, and the severe degree of congestion of the vascular bed are probably the most important. Other contributing factors may be the presence of severe hepatosplenomegaly or minute thrombo-embolic phenomena of the pulmonary circulation.

Hemorrhagic manifestations have long been recognized as part of the clinical picture in this dyscrasia. Although the figures given vary widely in the actual frequency, it is probable that this merely reflects what the observer chose to include as evidence of increased bleeding tendency. On closer scrutiny one readily sees that some writers included all hemorrhagic manifestations,11 and others just certain ones, probably the more severe. Thus, Lawrence et al., 18 who later in the same publication recognize this as a common manifestation of the disease, report cases totaling only 10%, but do not allude to any patients with hematuria or prolonged bleeding from tooth extractions, gums and minor injuries. Wasserman 17 clearly states that his figures do not include these minor hemorrhagic manifestations, and arrives at a similar figure of 16% in 270 cases. We believe that all these symptoms, when definitely present, should be included, since they are related to the fundamental disorder. On the other hand, we considered "easy bruisability" usually an unreliable observation, and therefore it was excluded. Videback's 16 figure of 59% is much higher than any other, probably because it represents data collected during follow-up of cases not under regular or effective control.

Constipation was present in four of the nine cases of Osler's original publication,<sup>3</sup> and he considered it to be an important manifestation of this condition. Recently, however, it has not been stressed in the literature. Although we encountered this less commonly than did earlier observers, it was a relatively frequent complaint and often quite severe.

Visual disturbances were uniformly reported by most observers, with close agreement as to frequency. Scotomata (often colored) and blurring of vision were the most common complaints. It should also be appreciated that other symptoms relating to the eyes, such as burning and lacrimation, were responsible for an additional 15% of ocular manifestations.

Abdominal pain was also a prominent symptom and, as previously mentioned, was quite often responsible for first bringing the patient to medical attention. Peptic ulcers, mesenteric thromboses, congestion of the liver, and pain in the region of the spleen possibly due to infarctions, traction of the splenic pedicle, or mechanical pressure, have been incriminated as possible factors for producing this complaint.<sup>10, 44</sup>

Paresthesias, mostly numbness and tingling of the extremities, were reported by several observers and, on the average, were present in 31% of the cases.

Thrombotic manifestations are a well recognized complication of this disorder. There was fairly close agreement by most investigators on the frequency of their occurrence. It is interesting to note that our average of

26% was exactly the incidence reported in two other series not included in the table. 16, 17 A breakdown of our figures with respect to specific location of the vascular occlusion revealed that 12% of them occurred as thrombophlebitis of the extremities, and 9% involved the cerebral and 2% the coronary arteries. (In three cases more than one site was involved.) These figures are almost identical with those described by the California group. 18

Perhaps one of the most nearly unique symptoms to be found in polycythemia vera is the presence of a peculiar form of pruritus which is aggravated by exposure to heat, especially bathing with hot water. In our own cases, this unusual description was given by half of the patients who complained of pruritus. Its presence has recently been emphasized and particularly discussed with reference to its value in differential diagnosis from the secondary polycythemias and the generalized, constant itching of Hodgkin's disease and lymphosarcoma. The over-all average frequency of pruritus was 23%.

Weight loss is a symptom not frequently mentioned in this disease. It was found to be present in 20% of our patients. In one of these, more fully described later, a hypernephroma was also present. We included in this group only those who lost more than 20 pounds in one year in the absence of dietary or diuretic regimens. The presence of hypermetabolism <sup>45</sup> and the resemblance of this disease to chronic granulocytic leukemia, both of which will be discussed subsequently, make this a not unexpected finding.

Chest pain, mostly precordial in nature, was present in about 16% of all the cases. We found it present in seven women as well as 10 men, often in the classic clinical picture of angina pectoris. Myocardial and pulmonary infarctions are other possible causes of this symptom in polycythemia vera.

Syncope is another neglected clinical manifestation, although it has been described in case material from the literature. 10, 13 Transient episodes of loss of consciousness unaccompanied by other neurologic manifestations or residuals and frequently terminating a severe bout of vertigo were present in 8% of our cases. It should be noted that in five of these eight patients this event was responsible for bringing the case to medical attention. Although theoretically a small cerebral vascular accident in a "silent" area could be incriminated, it is more likely that a reversible form of cerebral anoxia was responsible.

All the symptoms discussed were also analyzed with respect to sex and age distribution, and no significant patterns were noted except that women in general tended to have more symptoms than men.

# PHYSICAL SIGNS

It is generally accepted that most of the physical findings in polycythemia vera are due to the characteristic increase in total blood volume and red cell mass. This has been invoked not only as the explanation for visible manifestations or vascular congestion but also for the hepatosplenomegaly present during the hypervolemic phase. <sup>17</sup>, <sup>18</sup>, <sup>20</sup>, <sup>21</sup> In the later, or spent, phases, extramedullary hematopoiesis has been held responsible for the gross enlargement of the liver and spleen which is often present. <sup>17</sup>

The physical signs in the present series which may be attributed to vascular congestion are listed with their relative frequency in table 3. Wiseman et al. 15 found conjunctival injection present in 38% of 108 cases. Abnormal color of skin and mucous membranes was present in 62% of their patients. Lawrence and co-workers in their large series 18 also reported an incidence of 62% for "ruddy cyanosis of the face, fingertips, nose, ears, lips or mucous membranes of the mouth and pharynx." Reinhard and his group 18 found plethora to be present in 83% of their cases, although retinal venules and conjunctivae were reported to be congested in only about 30%. These signs were present in every one of 20 cases reported by Dameshek and Henstell. 10

Table 3
Signs Related to Vascular Congestion in 100 Cases of Polycythemia Vera

Visible	Present	Absent	Not Mentioned
1. Facial plethora	78	17	5
Distended retinal veins     Peripheral vasodilatation and	63	30	7
cyanosis	63	20	17
4. Congestion of nasal and oral mucosa	64	23	13
5. Congestion of conjunctiva	62	19	19
Palpable			
6. Splenomegaly (palpable)	69	31	0
7. Hepatomegaly (palpable, 4 cm. or more)	48	52*	0

 $<sup>^{</sup>ullet}$  In 22 of these cases liver was palpable from 1 to 3 cm. below the right costal margin in the midclavicular line.

Figure 2 shows the variation in size of palpable hepatomegaly and splenomegaly in our patients measured below the costal margin at the mid-clavicular line. The frequency with which enlargement of these organs was reported by several authors is listed in table 4. For palpable splenomegaly, the over-all average value obtained, as well as that reported by each of three large series, is in close accord with our experience. The variations reported for palpable enlargement of the liver are considerable. Sohval <sup>21</sup> states that in about two thirds of their 60 cases the liver was palpable, while in half it was moderately or markedly enlarged. Although this coincides with our findings, others have reported this finding in about one third of the cases, and in one Scandinavian series <sup>16</sup> an incidence of 7% is listed. The observer's differences in interpretation of hepatomegaly may be the principal reason for these variances. We do not mean to imply from our data in figure 2 that we consider a palpable liver, even to an extent of 2 or

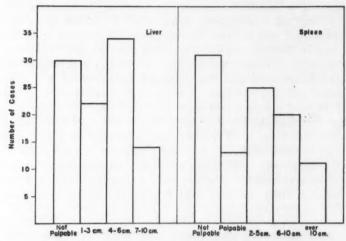


Fig. 2. Variation in size of liver (left) and spleen (right) in 100 cases of polycythemia vera at time of diagnosis. Measurements taken below the respective costal margins at the midclavicular line.

3 cm., to be necessarily an abnormal finding in this age group. We therefore included in table 4 only livers which were palpable 4 cm. or more from the costal margin at the midclavicular line as representing definite hepatomegaly.

The blood pressure in polycythemia vera is frequently elevated.<sup>20, 25</sup> A blood pressure greater than 150 systolic and/or 90 diastolic was present in 46 out of 94 cases. This incidence of 50% agrees exactly with that reported by two other observers <sup>10, 18</sup> using the same criteria. This finding was present in 67% of the females and in only 38% of the males. In all cases the values used were not necessarily the highest recorded or the ones listed on admission, but rather those representative of the stable level before therapy.

TABLE 4
Hepatosplenomegaly in Polycythemia Vera

In	stitution Reporting	Total No.	Splenomegaly		Hepatomegaly	
-11	stitution Reporting	of Cases	Number	Per Cent	Number	Per Cent
Rigshospitale	et, Copenhagen, Denmark <sup>16</sup>	125	60	48%	9	7%
	niversity, Columbus <sup>16</sup>	108	66	61%	16	15%
University of	California, Berkéley <sup>18</sup>	159	105 85 49 28	66%	16 52 38 30	33% 31% 50%
Mayo Clinic,		124	85	68%	38	31%
Mt. Sinai Ho	ospital, New York <sup>21</sup>	. 60	49	80%	30	50%
	University, St. Louis <sup>18</sup>	30	28	93%	8	27%
	Iospital, Boston <sup>10</sup>	20	16	80%	15 48	75%
University H	100	69	69%	48	48%	
Totals	Number of Cases Per Cent	720	478	66%	216	30%

Enlargement of the spleen was present with equal frequency in the hypertensive and nonhypertensive cases. There was normal sinus rhythm in all but six of the patients at the time of diagnosis. Five of these exhibited varying degrees of premature ventricular contraction, and one patient had auricular fibrillation. One additional patient developed auricular fibrillation later in his course. Cardiomegaly was present by percussion in nine cases, and in six additional ones it was reported roentgenographically. All but two of these patients had elevated blood pressures. One showed an increased cardiac output on catheterization, and the other had an erythrocyte count of 12,000,000, the highest in the present series, with an hematocrit of 73.5%. Heart murmurs were present in 40 patients. All of these were systolic, and in no case was the diagnosis of organic valvular disease made.

In most cases the chest was described as clear to percussion and auscultation. Some of the older patients had slight to moderate hyperresonance and prolongation of breath sounds. Basilar râles were present in seven cases, and in all of these hepatosplenomegaly was present in moderate to marked degree. In one case, described below, bilateral pleural effusion was present. Sternal tenderness was present in 12 patients and absent in 23. In the remaining cases, no statement was recorded.

Vascular disease of the extremities was present in 28 cases, ranging from varicose veins to such trophic changes as stasis dermatitis and ulcerations. A similar incidence is reported by Dameshek and Henstell.<sup>10</sup> In 12 of our patients active phlebitis was present. In three cases (not included above), ankle and leg edema alone was present. One of these was a 34 year old man who, in addition to polycythemia vera, had hypertensive cardiovascular disease with bilateral pleural effusion and ascites, possibly on the basis of chronic glomerulonephritis. In 46 cases the extremities were satisfactorily described as normal, and in the remaining 39 the notes on this examination were incomplete. Clubbing of the fingers or toes was not demonstrable in any of our cases.

Dermatologic findings in polycythemia vera have been described. These tend to be nonspecific and are said to regress with treatment.<sup>18</sup> Fourteen of our cases had skin abnormalities, and in five the lesion was described by a dermatology consultant as acne rosacea.

Neurologic manifestations were evident in eight individuals. Five showed acute or residual findings attributable to a cerebrovascular accident involving the pyramidal tracts. One case had chorea-athetoid movements with speech impairment, another had generalized arteriosclerosis with a Parkinsonian tremor, and the last presented a Bell's palsy. The presence of Parkinson's disease <sup>18</sup> and chorea <sup>26</sup> in polycythemia vera has been described.

## ASSOCIATED DISEASES

Peptic ulcer was present in six of our patients. In five it was in the duodenum and in one it was pyloric. At least four other cases had typical

epigastric pain relieved by milk and alkali, but no ulcer could be demonstrated radiologically. Gastrointestinal series roentgenograms were performed freely in several other instances where the slightest indication existed and were negative in all cases. In the literature a prevalence of peptic ulcer of 7 to 23% has been reported.<sup>8, 10, 18, 17, 18, 27</sup>

In 1945 Tinney and co-workers <sup>28</sup> reviewed the previous literature on the association of gout with polycythemia vera and added eight cases of their own, all in men. Other subsequent reports have varied from a prevalence of 1.9% <sup>17</sup> to 14%. <sup>49</sup> It has been suggested that it is more common in the myeloid metaplasia or spent phase of the disease. <sup>17, 29</sup> A recent study with N<sup>15</sup>-labeled glycine seems to indicate that the pathways of biosynthesis of uric acid in primary gout differ from those of gout occurring in association with polycythemia, although clinically the two are similar. <sup>30</sup> Gout was present in six of our cases, five men and one woman. A uric acid determination was recorded in 28 patients and was elevated over 5.0 mg./100 ml. in three females and over 6.0 mg./100 ml. in four males. Hyperuricemia is said to occur in 27 to 33% of patients with polycythemia vera. <sup>17, 40</sup> Three of the patients with gout (two men and one woman) had an elevated serum uric acid by these standards, and in one additional male a borderline value of 5.6 mg. was obtained.

The occurrence of hypernephroma in association with polycythemia vera has been reported in several cases. 16, 18, 31, 45, 72 In our group of cases a diagnosis of kidney tumor was made clinically in one patient. The presence of a right renal mass suggestive of a neoplasm on retrograde pyelography and multiple nodular pulmonary metastases, which were thought by the radiologist to arise from a hypernephroma, were the basis for this diagnosis. In addition, the patient gave a history of hematuria. Investigation of the lower urinary tract by cystoscopy was negative. There had been a 35-pound weight loss, and the patient died at home three months later after a further weight loss of 68 pounds. The total duration of his illness was one year. Unfortunately, a tissue diagnosis is not available.

The relationship of leukemia to polycythemia vera has been extensively analyzed by many authors. This association will be discussed in the section on course and therapy,<sup>39</sup> along with the problem of myelofibrosis and myeloid metaplasia. However, it might be appropriate to mention here that the combination of multiple myeloma and polycythemia reported in the literature <sup>40</sup> was not encountered in our series.

# LABORATORY FINDINGS

Whenever possible, the laboratory data used were those obtained at the time of the original diagnosis. Unfortunately, this could be done for only about two thirds of the cases. The remainder, however, were nearly all in hematologic relapse at the time the data were recorded.

Erythrocyte Count: The erythrocytes are characteristically increased in number in polycythemia vera. The distribution encountered in our group is shown in figure 3. There was essentially no difference in the curves obtained for males and females, and the highest count recorded was 12,000,000. Most writers agree that the greatest number of counts fall between 6,000,000 and 9,000,000. The strength of the various series are undoubtedly due to such factors as the number of cases previously treated, the severity of the disease in the cases chosen, and individual laboratory variations.

Hemoglobin: The majority of patients had hemoglobin values between 16 and 25 gm., as shown in figure 3. It is interesting to note that 75% of the patients with low values were those whose determinations were made subsequent to the original diagnosis by the referring physician. This prob-

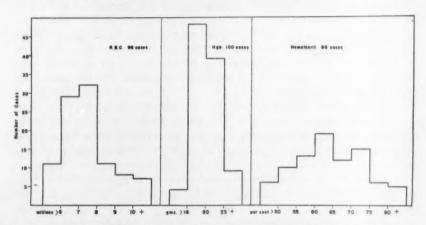


Fig. 3. Histograms showing distribution of erythrocyte counts, hemoglobin and hematocrit determinations recorded at or about the time of diagnosis of polycythemia vera.

ably reflects the effect of treatment on this determination. The same occurrence was not so evident in erythrocyte counts, which is in line with the well known fact that a hypochromic microcytic polycythemia develops in patients treated by repeated phlebotomy.

Hematocrit: The packed red cell volume distribution is presented in figure 3. The highest value obtained was 83%. Almost all the values under 55% were determinations made upon admission to the hospital and not at the time of the original diagnosis.

Red Cell Indices: Calculation of the mean corpuscular volume was possible in 68 cases. For the mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular hemoglobin, data were available in 74 and 91 cases, respectively. About one quarter of the patients with MCHC values showed hypochromia, probably as a result of previous phlebotomy or

other blood loss. The majority of patients, however, were within the normal range (figure 4).

Reticulocyte Count: In 45 patients a reticulocyte count was performed by smearing a drop of fresh blood on a slide prestained with cresyl blue. A value of over 3% is considered to be elevated in this laboratory. Increased reticulocyte counts were present in eight patients. In six of these the determination was not performed at the time of diagnosis, and may represent a response to phlebotomy therapy.

Erythrocyte Sedimentation Rate (Wintrobe): The erythrocyte sedimentation rate was zero in all the patients except one. A value of 16 mm. in one hour was recorded for the patient with coexistent hypernephroma three months before his death. His red blood cell count was 6,390,000 and his hematocrit was 45% at this time.

Leukocyte Count: The first investigators of this disease did not appreciate the fact that an elevated leukocyte and platelet count was part of the blood picture. Turk <sup>41</sup> in 1904 observed the presence of granulocytic leukocytosis, and subsequently this has been readily recognized and confirmed. It also became obvious that polycythemia vera was often associated with leukemoid blood pictures or even granulocytic leukemia. This usually appears in the later stages of the disease.<sup>17</sup>

Figure 5 shows the leukocyte counts and distribution in the patients we studied. We wish to emphasize that, while the leukocyte count in polycythemia vera may be extremely high, the majority of cases have only a slight elevation. Thus, as in other series, 10, 11, 13, 18 the mode is between

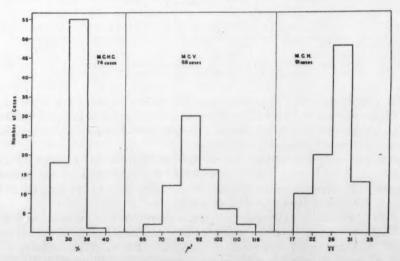


Fig. 4. Histograms showing distribution of red cell indices calculated at or about the time of diagnosis of polycythemia vera.

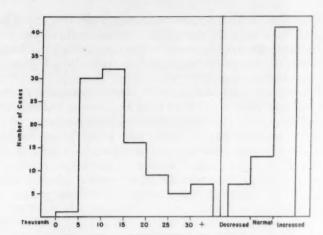


Fig. 5. Distribution of leukocyte counts (left) and estimates of number of platelets present (right) observed at or about the time of diagnosis of polycythemia vera.

10,000 and 15,000, while about 60% of the cases can be shown to fall in the 10,000 to 20,000 range. 11, 18, 15 Although this increase in the granulocytic series usually occurs as a neutrophilic leukocytosis, the eosinophils and the basophils were also slightly increased in some instances. A remarkable example of this phenomenon was seen in a 60 year old woman who had 50% eosinophils and a total white cell count of 13,000 without the presence of any of the more usual causes of eosinophilia. Cases of unexplained eosinophilia, even to this degree, are sometimes encountered without polycythemia vera, but it is tempting in this instance to accept this as a manifestation of the panmyelosis.

Thrombocytes: The increase in circulating platelets which is frequently observed is generally taken to be further evidence of the increased activity of all bone marrow elements. Although actual platelet counts were performed in only 33 cases, in an additional 34 patients an evaluation of the quantity of platelets present on blood smears was made. This was reported as increased, normal or decreased. A value of over 300,000 platelets was considered to be elevated, and one of less than 200,000 was listed as below normal. Figure 5 illustrates the number of platelets in all 67 patients.

Bone Marrow: Bone marrow aspiration was performed in 21 cases. Increase in the erythroid elements was present in 11 of these. Transition from a leukemoid picture to granulocytic leukemia was reported in one. In another case several attempts were unsuccessful. The patient at this time had a peripheral red cell count of 6,320,000, a hemoglobin of 16.5 gm. and a white cell count of 14,000. These findings may be evidence of the localized nature of early myelofibrosis. 60

Basal Metabolic Rate: The basal metabolism of 27 patients was meas-

ured. Figure 6 shows the distribution obtained, which ranged from minus 1 to plus 70. Mild to moderate elevation was present in the majority of cases, while of the remainder about half were within normal limits and half showed marked elevation. Increased basal metabolic rates in polycythemia vera have been reported by others. 10, 20, 46

Renal Excretory Function Tests: The urine was tested for albumin in 87 cases, and in 46 patients (53%) a trace or more was present. Fourteen patients had intravenous phenolsulfonphthalein excretion tests, and in seven of these excretion values of 45% or less were present after two hours. A serum nonprotein nitrogen determination was done in 74 patients and averaged 42 mg./100 ml. A value of 50 mg. or above was obtained in nine cases. In only one of these was the blood pressure elevated above 150 systolic and/or 90 diastolic. The average age of these patients was 54 years, and all but one were men.

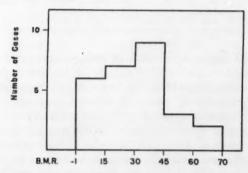


Fig. 6. Basal metabolic rate in 27 patients with polycythemia vera before myelosuppressive therapy.

Chest X-ray: Roentgenograms of the chest and interpretations by the radiology department were available in 87 cases. "Prominent vascular markings" or "congestion" was reported in 60% of these. Other positive findings, all previously mentioned, included the cases with cardiomegaly, multiple nodular metastases suggestive of hypernephroma in one patient, and bilateral pleural effusion in another. Except for the occasional presence of a calcified hilar node and minimal apical scarring, the remainder were within normal limits.

Electrocardiograms: The electrocardiographic findings in 63 cases showed no specific pattern. In several cases changes suggestive of coronary artery disease consistent with this age group were reported. Twenty-one patients had normal electrocardiograms.

Arterial Oxygen Saturation: In the great majority of patients with polycythemia vera the arterial O<sub>2</sub> saturation is within normal limits or slightly reduced.<sup>18, 43</sup> Cases have been reported with moderate to severe arterial

unsaturation. 42, 48, 47 Various mechanisms have been suggested by these authors to explain these findings. Because a slight reduction in arterial O<sub>2</sub> saturation may be present in healthy individuals over 50 years of age, 48 this finding could occur in patients with polycythemia vera who usually are in this age group. 43 More severe degrees of arterial unsaturation may be due to coexistent pulmonary disease, damage to the medullary respiratory center, poor ventilation of perfused areas, reduction of the capillary bed by emboli or thromboses, with impaired diffusing capacity, reduction of total alveolar ventilation from the effects of vascular congestion, and increased blood

viscosity in both the lungs and the muscles of respiration. 42, 48, 47

Arterial oxygen saturation was measured in 15 patients by means of the Van Slyke-Neill apparatus. In nine cases a value of 94% or higher was obtained. Five individuals had determinations of 90 to 93%, and in one man a saturation of only 83% was present at rest. This patient had a blood pressure of 210/110 mm. of Hg but no cardiomegaly. There was splenomegaly but no hepatomegaly or evidence of heart failure. The chest was increased in A-P diameter, and a few moist râles were present. Although the chest x-rays showed no evidence of lung disease, pulmonary function studies revealed the presence of fairly severe emphysema with some degree of reversible bronchospasm. The residual volume/total lung capacity ratio was 55.8%, against a predicted value of 30.8%, and the timed vital capacity was 55.3%, 65.8% and 73.9% for one, two and three seconds, respectively. In evaluating the whole clinical picture, the hematology and pulmonary consultants agreed that the functional studies and reduced saturation could account for a degree of secondary polycythemia, but that the unusually high red blood cell count (7,380,000) and splenomegaly (4 cm.) in the absence of hepatomegaly or heart failure made the presence of both primary and secondary polycythemia likely.

Blood Volume: Blood volume determinations were carried out in seven

patients and in all were elevated, with a range of 83 to 133 ml./kg.

#### COMMENTS

In clinical medicine, special attention should be directed to those conditions where early diagnosis significantly benefits the patient. It is therefore good practice to be aware of the less common diseases, in which early recog-

nition and treatment may prevent irreparable damage or death.

Much is still to be learned about polycythemia vera, particularly its etiology, which remains obscure. There is no question, though, that many individuals live active, productive lives for several years, especially when under proper supervision and management. Because of its insidious onset, the condition may exist for years unrecognized by the patient or the physician. If care is taken to establish its presence when apparently insignificant manifestations are present, the disease will less often present itself as a

thrombotic or hemorrhagic disaster. Particular note should be made here that abdominal pain is a close second to the equally nonspecific weakness as a presenting complaint. Surgical intervention may prove fatal because of the increased thrombotic or bleeding tendencies so commonly present.

In reviewing the panoramic array of symptoms which may be present, one can easily see that many clinical conditions may be mimicked. In this respect polycythemia vera rivals even the all-encompassing collagen diseases. Neurologic and psychiatric symptoms are particularly frequent. Vascular disease of the extremities is also quite common. In the differential diagnosis and evaluation of a patient with hypertension, polycythemia vera should be considered. One may easily dismiss a ruddy patient with an elevated blood pressure and dizziness, headache scotomata, dyspnea and an emotional overlay as having "essential hypertension." Attention is called to constipation and weight loss as two symptoms not often mentioned in the recent literature. Although not extremely common, benign syncope is probably also more frequently encountered, especially among the presenting symptoms, than is generally realized. Probably the most nearly unique symptom described is a peculiar and persistent pruritus which is intensified by bathing with warm water. Considering the possibility that this disease may be present is unquestionably the hardest step in making the diagnosis. Once the suspicion has been aroused, supporting evidence may be searched for in the physical and laboratory examinations.

Two helpful general conclusions that can be reached from our data on the physical findings are: (1) each particular sign related to vascular congestion (whether visible or palpable) can be expected to be present in about two thirds of the patients, and (2) every case at the time of the original diagnosis presented one or more of these findings. Therefore, in any given case the manifestations of the existent hypervolemia could be dependent upon the distribution and distensibility of the particular vascular bed. One patient may at first more readily accommodate the increase of blood volume in his liver, another in his skin, and so on. As the process continues to the full-blown polycythemic stage, an increasing number of physical findings will be present. Hypertension was frequently present, in some cases associated with cardiac enlargement, but the presence of other significant objective heart findings was not common in our patients. The cardiac arrhythmias, the electrocardiographic abnormalities and murmurs which were present are not particularly unusual for patients in this age group. At the bedside, absence of clubbing of the fingers may be an extremely important finding in differentiating this from secondary polycythemia. Finally, the not unusual occurrence of sternal tenderness, which is also present in most patients with chronic leukemia, is of interest.

The importance of the laboratory data in confirming the diagnosis rests upon establishing the presence of an increased red cell mass and a normal arterial oxygen saturation. For practical clinical purposes this increase is usually reflected (in the untreated case) in an elevation of the red cell count, hemoglobin and hematocrit. The red cell indices for the most part are normal. The reticulocyte count usually is not elevated unless bleeding has occurred. This would suggest that the normal regulatory factor(s) are still operating but at an elevated level. Evidence of panmyelosis, which is often present, may furnish extremely valuable supportive evidence for the diagnosis.

As usual, however, it is not the classic picture but the atypical one that causes difficulty in diagnosis. It is therefore important to determine whether bleeding, either spontaneous or therapeutic, could be responsible for a normal blood count in the suspected case. Likewise, one may account for reduced levels of arterial oxygen saturation on the basis of the coexistent complications already discussed.

An important and challenging facet of this disease is its frequent association with certain seemingly unrelated conditions, the significance of which still remains largely speculative. Thus, peptic ulcer has been attributed to congestion or other circulatory disturbance of the involved area. The frequent elevation of uric acid levels does not explain why gout occurs in certain patients and not in others, or why it tends to be more frequent in the later stages of the disease. Is this merely a function of time, or does a basic change in the metabolic pathways develop? It may be conceivable to assume the presence of a familial or other etiologic predisposition to these conditions, which is brought to the clinical level by an overload of the systems involved. Another very interesting combination is that of polycythemia vera and hypernephroma, especially since some reports indicate that a removal of the tumor is followed by reduced blood counts. Little is known about the endocrine function of the kidney. The possibility that it is a source of a circulating bone marrow-stimulating factor, erythropoietin, has been suggested but is not as yet established. 78, 74

## SUMMARY

In the last 15 years a renewed interest in polycythemia vera, kindled by the advent of radioactive phosphorus, has produced many excellent reports dealing with the clinical evaluation of this isotope. We have attempted to compare the pertinent data presented by some of these authors with those of our own series of 100 cases, to provide a unified and more nearly complete clinical picture of the disease in the erythremic stage.

The varied manifestations and laboratory findings early in the course of the disease have been particularly stressed in an effort to foster recognition before severe and often irreversible complications have set in. Mention is made of helpful findings and certain pitfalls which may be encountered in arriving at the diagnosis.

The association with other conditions, such as peptic ulcer, gout and

hypernephroma, is reaffirmed, and the need for further research in these fields is briefly discussed.

#### SUMMARIO IN INTERLINGUA

In le curso del passate 15 annos, le disponibilitate de phosphoro radioactive ha resultate in le publication de multe excellente reportos de successo in le tractamento de polycythemia con le isotopo mentionate. Viste que le prompte diagnose sequite per le prompte initiation del tractamento de iste condition pote prevenir irreparabile noxias o mesmo le morte del patiente, il es importante esser familiar con su varie manifestationes. Le presente reporto concerne un serie de 100 casos studiate al Hospitales del Universitate Wisconsin e presenta un comparation de datos pertinente con illos trovate in altere grande series, con le objectivo de obtener un unificate e plus approximativemente complete delineation del morbo in su stadio erythremic.

Le etate medie al tempore del diagnose esseva 54 annos. Symptomas relationabile a polycythemia habeva essite presente, al media, pro duo annos ante le diagnose. Le proportion inter masculos e femininas esseva 1 a 8. Nulle predominantia particular esseva notate inter le gruppos formate secundo criterios ethnic o occupational. Le duo plus commun symptomas initial esseva debilitate e dolores abdominal. A parte iste duo, discoperta incidental esseva responsabile pro le recognition de un plus grande procentage del casos que le altere manifestationes de character plus tosto classic. In 541 casos reportate ab sex major clinicas, debilitate, fatiga, e mal de capite esseva le symptomas le plus commun, sed le manifestationes de iste morbo es si variate que illos pote simular numerose commun conditiones clinic. Le constatationes physic es le resultato de augmentos del total volumine de sanguine e del massa de erythrocytos. Splenomegalia e altere signos relationate a congestion vascular esseva presente, cata un, in circa duo tertios del casos, sed omne caso habeva un o plures de iste signos al tempore del diagnose. Investigationes laboratorial revelava le ben-cognoscite constatationes de augmentos del total volumine de sanguine, del valores erythrocytic, leucocytic, e plachettal, e del intensitate del metabolismo basal. Aspiration de medulla ossee es de valor pro determinar le transition a leucemia o myelofibrosis.

Difficultates particular in establir le correcte diagnose pote esser incontrate quando sanguination (spontanee o therapeutic) es responsabile pro normal numerationes del cellulas sanguinee. Similemente, varie complicationes es responsabile pro le facto que un reducite saturation oxygenic in le sanguine arterial non es un constatation incommun.

Le association con altere conditiones—incluse ulceres peptic, gutta, e hypernephroma, es reaffirmate. Es sublineate le desiderato de studio additional in iste campos.

## BIBLIOGRAPHY

References for Part I and Part II of this article are combined on pages 1214-1216.

# POLYCYTHEMIA VERA. II. COURSE AND THERAPY \*

By Paul Calabresi, M.D., and Ovid O. Meyer, M.D., F.A.C.P., Madison, Wisconsin

THE successful use of radioactive phosphorus for the treatment of polycythemia vera was first reported by Lawrence 9 in 1940. By 1946 there was substantial agreement that this was the treatment of choice for this condition. 18, 14 Since that time the general availability of this isotope to larger medical centers has allowed the study of appreciable numbers of cases by single clinics. From this opportunity a better understanding of the course and complications of this disease process has come forth. The physical and biologic characteristics of P32, as well as the rationale for its use in polycythemia vera, have been well described. 13, 70 However, certain vital information on the natural course of polycythemia does not seem to be available.15 Moreover, in his recent monograph Lawrence 50 states that "there is little information available on the prognosis after treatment" and that "there are not many reports in which adequate follow-ups or analysis of end results in large groups of patients are given." In the preceding paper 51 we described in some detail the clinical and laboratory findings encountered in 100 cases studied at the University Hospitals. We are now reporting on the course of these patients treated with radioactive phosphorus.

# CASE MATERIAL AND TREATMENT SCHEDULE

Of the 100 cases originally studied, 51 up-to-date follow-up information was obtained in 97 patients. Although P32 has been used in this clinic since 1946, the onset of the disease in some of the cases included in this series precedes this date by several years. The longest course (case 97) was 23 years.

Therapy in this clinic prior to the use of P82 consisted mainly of venesections, Fowler's solution and phenylhydrazine. No attempt is made to evaluate the efficacy of these regimens, since this information is not complete. With the advent of P82 the following general treatment plan was adopted. The initial dose, ranging from 2.0 to 10.0 millicuries (average, 6.0 mc.), was individualized according to body weight and erythrocyte count for each

<sup>\*</sup> Received for publication March 28, 1958.

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patient. The drug was administered orally in all but six instances, where the equivalent dose (75% of the oral dose) was injected intravenously. It has been the tendency in recent years to use smaller initial doses. The patient's hypervolemia was reduced immediately by a series of phlebotomies (500 c. c. each) until the erythrocyte count fell below 6,000,000. Appointments were scheduled in the outpatient clinic at six weeks, three months and six months from the beginning of therapy. Depending upon the response obtained, the individual was subsequently seen at three- to six-month intervals. Routine laboratory procedures performed at these visits were designed to conform with the demands of an outpatient clinic, and consisted of erythrocyte counts, leukocyte counts and hemoglobin determinations. Other studies were requested when indicated.

A patient was considered to be in good control when his erythrocyte count did not exceed 6,000,000 and he was asymptomatic. Our subsequent evaluations on duration of remissions are based on these criteria. To maintain this control a combination of phlebotomies and P<sup>32</sup> was used as needed. Unfortunately, many of the phlebotomies were performed by the patient's private physician, often in distant communities, and this information is not readily available. All the P<sup>32</sup>, however, was administered at the University Hospitals.

# CAUSE OF DEATH

Of the 97 patients whose present status is known, 28 are dead. Five of these died at the University Hospitals, and in four postmortem examinations were performed. In the remaining cases the information relating to the cause of death was obtained from personal communications with the attending physicians or, when this was not possible, from the death certificate. These and other pertinent data are recorded in table 1.

Among the patients who have died, the male: female ratio was similar to that of the total series, as was the duration of preceding symptoms. The median age at death was 65 years. The duration of the total course in this

group averaged eight years from onset of the disease.

Six patients, or 21% of those dead, died with chronic granulocytic leukemia. This corresponds well to the figures given by Lawrence <sup>50</sup> for leukemic deaths in his series (16 leukemias in 73 deaths). Much discussion has centered about this "complication" of polycythemia vera, particularly with respect to P<sup>82</sup> therapy. The potential leukemogenic effects of ionizing radiation are becoming increasingly obvious, and the capacity of P<sup>82</sup> to produce leukemia in animals has been reported. <sup>52</sup> However, the occurrence of leukemia in polycythemia vera prior to radioactive phosphorus was well known, <sup>12, 58, 54</sup> particularly in long-standing cases. <sup>55</sup> In 163 cases treated without P<sup>82</sup>, Tinney et al. <sup>56</sup> found a leukemic picture responsible for 62% of the deaths in patients surviving over 10 years. The total course of the patients who succumbed with leukemia in the present series averaged 11.7

years. It has also become increasingly popular in recent years to speak of polycythemia vera and leukemia as manifestations of a broader group of related conditions known as the "myeloproliferative syndrome." <sup>58, 59, 60, 61</sup> Among these is included myelofibrosis with myeloid metaplasia, <sup>69</sup> which was

TABLE 1
Data on Patients Who Died

Case No.	Sex	Age at Death	Post Mortem	Cause of Death	In Remission at Time of Death	Duration of Course on P <sup>32</sup> (yrs.)	Total Course (yrs.)	Total Dose of P <sup>32</sup> (in mc.) Orally
2	M	48	-	Hepatic failure (Laennec's cirrhosis)	Yes	414	41/4	7
13	M	69	*******	Bronchopneumonia		44	51	8
14	M	43		Myocardial infarction	Yes	14	24	12.4
16	F	66	Yes*	Myeloid metaplasia and myelofibrosis	No	2	91	13
23	M	69	_	Myocardial infarction	Yes	74	121	5++3
24	M	72	-	Cerebrovascular accident	Yes	71 31	31	20
26	F	79		Myocardial infarction	Yes	5	61	5++10
27	M	72		Myocardial infarction	No	3 days	7	7
28	M	55		Hypernephroma	Yes	1	11	8
31	M	61		Myocardial infarction	Yes	71	101	27
38	F	75		Pulmonary embolism	Yes	4	8	6
42	F	56	_	Chronic granulocytic leukemia	No	8	121	10+47
43	F	73	-	Cerebral thrombosis	No	9	224	10+57
52	M	34	-	Chronic glomerulo- nephritis	-	1/4	34	5
55	M	48		Lobar pneumonia	Yes	3	10	28
58	M	66		?	_	16 days	4	5
65	F	65	_	Cerebral hemorrhage	_	15 days	1	5
67	M	62	-	Acute pyelitis and septicemia	No	5	51	43.2
73 -	M	58	Yes*	Chronic granulocytic leukemia	No	8	131	83
75	M	61	-	Chronic granulocytic leukemia (C.V.A.)	No	1 1	101	11
82	F	67	-	Myelofibrosis and myocardial infarction	No	11	41	18
84	M	55	-	?	Yes	41	51	10
86	M	69		Hepatorenal syndrome	No	3	7	11
87	M	73		Chronic myocarditis	Yes	51	141	19
89	M	84	*	Hypoplastic anemia (bronchopneumonia)	Yes (Tox)	1	11	8
92	M	62	-	Chronic granulocytic leukemia	Yes	13	41	8
93	M	64	Yes*	Chronic granulocytic leukemia (C.V.A.)	Yes	51	63	26
97	M	64	Yes*	Chronic leukemia	Yes	6	23	19

\* Death occurred at University Hospitals.

† Intravenous dose.

present at time of death in two of the other cases here reported. The similarity and interrelationship of these conditions have led to the opinion that leukemia and myelofibrosis with myeloid metaplasia are not strictly complications but merely later stages of polycythemia vera.<sup>17</sup> It should be noted, however, that Valentine et al.<sup>75</sup> have reported metabolic differences, particu-

larly in unit alkaline phosphatase activity, in the leukocytes of these diseases. The significance of these observations is at present poorly understood.

Myocardial infarctions were responsible for six deaths (one in a patient with myelofibrosis), and cerebrovascular accidents were fatal in five, two of these occurring as terminal events in the aforementioned chronic leukemias. Because of the frequency of these conditions in this age group, the relative rarity of coronary thrombosis in polycythemia vera, 44 and the fact that the polycythemic process was well controlled in six of these patients at time of death, it would be difficult to conclude that these episodes were exclusively thrombohemorrhagic complications of the primary disease.

Infections were present in four cases, and there were two postoperative deaths, one due to pulmonary embolism and the other to liver failure. We noticed no association with malignant disease, other than hematologic, except for a case of hypernephroma previously discussed.<sup>51</sup> One patient (case 89) died of hypoplastic anemia and will be considered under toxic complications of radiophosphorus.

# SUCCESSFUL REMISSION

A remission, as designated by the previously outlined criteria, was considered successful when it was sustained for one year or longer. In this way we avoided including temporary remissions caused only by intensive phlebotomies. Seventeen patients were excluded either because detailed information on their course was not available or because they have not yet been under treatment for a full year. In the remaining 80 cases, 92 successful remissions were observed in 67 patients. Two more have been followed for over one year on therapy and have been in remission for the last six months. Eleven individuals (14%) did not respond satisfactorily. They will be discussed in a subsequent section.

Table 2 contains the details of the dosage requirements of P<sup>32</sup> as well as duration of remissions and other pertinent data. It will be noted that an average of 7 mc. of P<sup>32</sup> was necessary to produce a remission. This dose did not seem to vary greatly for subsequent remissions. The average time interval necessary to obtain remission after administration of P<sup>32</sup> was five months. It should be emphasized that, since the patients were followed approximately every three months, this probably represents a slightly longer interval than was actually required for control. If this factor is taken into consideration, our findings would agree with the concept that the effect of therapy becomes manifest only as the destruction of the circulating erythrocytes is not being compensated by the depressed bone marrow.<sup>14</sup> It is because of this delay that phlebotomies should be performed at the onset of isotope therapy for more rapid relief of symptoms and to decrease the danger of thrombohemorrhagic complications.

Once a remission was obtained, approximately half of the patients required no additional maintenance P<sup>82</sup>. Those who had to be maintained on

Data on Patients in Whom Successful Remissions Were Effected TABLE 2

	No. of	<	Time Interval to	No. of Remission	Av. Duration	Av. Duration of Remission	Av. Duration of Remission of Remission of Remission	Av. Pm Required for	Ren	Remission Terminated by	erminat	ed by	No. of Remissions
	Remis- sions	Necessary to Obtain Remission	Remission (mos.)	Requiri no Pa f	without Pss (yrs.)	Maintenance M	Requiring Maintenance Ptt (mc.)	Maintenance (mc./yr.)	Sx	† RBC	RBC Sx & TRBC	Death	Still in Progress
	19	7.3	4.3	29	3.3	3.4	11.6	3.4	10	10	11	00	33
Second	23	6.7	7.4	12	2.6	2.5	8.7	3.5	-	3	3	4	12
remission hird remission	7	6.5	4.5	2	1.0	0	***	1	0	0	1	0	-
Fotals or Averages	92	7.0	5.0	43	3.0	3.2	11.0	3.4	11	00	15	12	46

Comparison of Findings before Therapy in Relation to Remissions Obtained TABLE 3

	Av. Spleen Size before	(in cm.)†	3	15
	Av. Duration of Disease before	Therapy (in yrs.)	2.6	4.9
		Very High (over 25.0 × 104)	4 (6%)	5 (45%)
erapy	Leukocytes	High (15.0–25.0 X 109)	(30%)	5 (45%)
nts before Th		Normal (5.0-15.0 × 10²)	43 (64%)	(10%)
Initial Blood Counts before Therapy	Erythrocytes	Very High (over 7.5 × 10°)	(20%)	5 (45%)
Initi		High (6.0-7.5 X 10*)	42 (62%)	(55%)
			Normal (4.2-6.0 X 10°)	(18%)
	Av.		53	26
	Sex	(M:F)	1.7:1	1.8:1
	Total No. of	Cases	29	11
			Successful remissions*	Inadequate remissions

\* Cases 42 and 43 included (successful remissions initially, then refractory—see text). † Measured below left costal margin at midclavicular line.



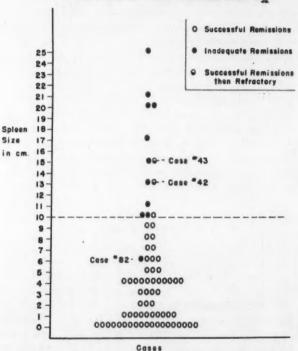


Fig. 1. Prognostic value of spleen size in predicting response to P<sup>an</sup> therapy. Each symbol represents one patient. Cases 42 and 43 (described in text) responded initially to therapy and later became refractory. Case 82 subsequently developed myelofibrosis. Measurements were taken below the left costal margin at the midclavicular line, and represent values obtained just before initiation of P<sup>an</sup> therapy.

the drug received an average of 3.4 mc. a year. In both groups the average duration of remission was about three years. That this figure may be appreciably increased with time can be presumed from the fact that in 46 patients a remission is still in progress. Of the other 21 cases, 12 died in remission, and seven have not had the opportunity to qualify for a subsequent full year under therapy. The two remaining patients (cases 42 and 43) are of special interest. They represent the only patients in the present series who responded initially to therapy and later became refractory after two previous successful remissions each. Despite repeated and relatively high doses of P<sup>82</sup>, they remained out of control until death, which occurred in one case three and one-half years later from cerebral thrombosis, and in the other four and one-half years later from leukemia (table 1). That this sequence of events was to be not entirely unexpected is indicated by certain findings at initiation of therapy (table 3 and figure 1). Both patients pre-

sented a very high leukocyte count and greatly enlarged spleens (case 42: white blood cell count, 38,000; spleen, 13 cm.; case 43: white blood cell count, 40,000; spleen, 15 cm.). The prognostic significance of this information with respect to the ability of P<sup>32</sup> to induce remission is discussed below.

# INADEQUATE REMISSION

A remission, as previously defined, was not induced in 11 cases. A summary of the pertinent data for these patients may be found in table 4. An average total dose of 33.1 mc. of radioactive phosphorus was administered over an average period of 3.7 years. These people then received more than double the amount of P<sup>32</sup> necessary to produce and maintain a successful remission in the first group. An attempt was made to determine whether any of the information available at initiation of therapy could be of prognostic significance. The data in table 3 show no difference in age and sex ratio of the two groups. There was a general tendency for the patients not obtaining successful remission to have more severe disease as determined from the peripheral blood counts. This was particularly evident when the leukocyte count was over 25,000, if it is considered that cases 42 and 43, described above, were included in the successful remission group. Possibly of most value in predicting the therapeutic success of P<sup>32</sup> is the spleen size before therapy. It can be seen from figure 1 that if a spleen is palpable

Table 4

Data on Patients in Whom Inadequate Remissions Were Effected

Case			Before Therapy		Total Dose	Duration			Spleen
Case No.	Age	Sex	RBC	WBC	of P <sup>32</sup> (mc.) Orally	Therapy (years)		Initial Size*	Change
9	70	M	Н	VH	27	2	Fair control	25 cm.	Slight decrease
16	63	F	H	VH	13	11	† Myelofibrosis and myeloid metaplasia	21 cm.	Slight increase
29	40	M	VH	VH	19	14	Fair control	10 cm.	Slight decrease
57	58	F	VH	H	61.2	9	Fair control	20 cm.	None
67	57	M	VH	H	43.2	5	† Acute pyelitis	10 cm.	None
68	45	M	H	H	41 -	1½ 9 5 5½	Fair controi	13 cm.	None
73	45	M	VH	VH	83	8	† Leukemia	20 cm.	None
75	52	M	H	VH	11	11	† Leukemia	17 cm.	Slight decrease
79	43	M	H	H	22	2	Fair control	15 cm.	None
82	63	F	Н	H	18	21/2	† Myelofibrosis and coronary thrombosis	6 cm.	Slight decrease
85	75	F	VH	N	26	21	Fair control	11 cm.	Slight decrease

$$H = High (RBC = 6.0 - 7.5 million)$$
  
(WBC = 15.0 - 25.0 thousand)

<sup>\*</sup> Measured below left costal margin at mid-clavicular line. † Died.

10 or more cm. below the costal margin the chances of obtaining a remission are poor. The average spleen size in the group showing poor response to therapy was 15 cm., as compared with 3 cm. in the other. Note should be made that, despite a relatively small spleen, case 82 was developing myelofibrosis and was probably in a relatively advanced stage of the disease. The importance of this factor is emphasized by the fact that in the cases where adequate remission was not obtained, the disease before therapy had existed for almost twice as long.

Five of these patients are dead, and in four of these leukemia or myelo-fibrosis was present. The remaining six may all be said to be in fair control. Of these, three are asymptomatic, and in no case does the erythrocyte count exceed 7,000,000. A decrease in spleen size was recorded in about half of the patients, including those who died. Thus, even though these cases did not meet the arbitrary requirements we established for successful remission, all derived some benefit from P<sup>32</sup>, and in some this represents significant improvement.

# LIFE EXPECTANCY

A survival curve for the 97 cases studied has been calculated according to the method employed by Lawrence.<sup>50</sup> For the sake of comparison, the onset of symptoms was adopted as the beginning of the disease in our series as well. This averaged two years prior to diagnosis, and only definite symptoms or signs related to polycythemia were considered. 51 The average age of onset of the disease in both groups was 52 years. It may be seen from figure 2 that the curve of the present series (median survival, 11 years) corresponds quite well to that of Lawrence's patients (median survival, 13.3 years). Both compare favorably with the cases reported by Videback, 16 that were treated with methods other than P32. In this series the average survival for the entire 125 cases was calculated to be 5.6 years. A survival diagram is also presented for 64 of these cases observed for at least 10 years, and we have attempted to reproduce this in figure 2. It will be noted that the median survival by this method is improved to 6.7 years. We used the higher figure in our comparison in an effort to equalize for the fact that duration of the disease in these patients was calculated from the time of diagnosis (average, 53 years of age).

In a comparison of these results, two facts must be emphasized: (1) an error of one or two or even more years may be introduced because of inability to determine accurately the starting point of the disease process, and (2) the close follow-up and supervision necessary in the patients treated with P<sup>32</sup> may not have been present in those treated by other means. It is impossible to estimate the importance of the latter factor in improving the prognosis of other forms of treatment. However, survival in the present series might have been improved if better coöperation from certain patients could have been enlisted.

It is of interest that patients with polycythemia vera treated with P<sup>32</sup> may expect to do as well as individuals afflicted with other chronic, medically treatable conditions of this age group, such as diabetes mellitus and pernicious anemia.<sup>12</sup>

# TOXICITY

The incidence of toxic manifestations observed was confined to excessive marrow depression. No nausea, vomiting, dermatitis or radiation sickness was observed. In two cases a significant transient depression of the peripheral blood elements was observed (case 43, a 60 year old woman: white blood cell count, 2,900; P<sup>32</sup>, 10 mc. intravenously; case 15, a 55 year old

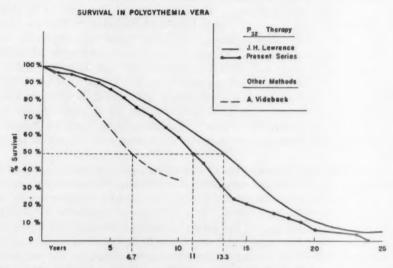


Fig. 2. Diagrammatic representation of survival in polycythemia vera in patients treated with P<sup>so</sup> and by other methods. For references and details see text.

woman: white blood cell count, 1,200, decreased platelets with petechiae and vaginal bleeding; P<sup>32</sup>, 10 mc. orally). Both patients recovered spontaneously within one month. A third patient (case 89, a 79 year old man) succumbed with hypoplastic anemia probably related to P<sup>32</sup> therapy. On February 11, 1948, he received an initial dose of 3 mc. of radioactive phosphorus orally. His erythrocyte count at this time was 9,990,000 and his leukocytes numbered 8,800. On April 15, 1948, his erythrocyte count was 5,500,000 and, despite a leukocyte count of 2,400, he was erroneously given an additional 5 mc. of P<sup>32</sup> orally. Subsequently his erythrocytes fell to 2,000,000 and his leukocytes to 1,900. He had thrombocytopenia and purpuric manifestations. Despite repeated transfusions and antibiotics he

died on August 1, 1948, with a drug-resistant bronchopneumonia. All three cases represent earlier experiences with this agent. In the first two a large initial dose was administered. Considerably smaller initial doses have been employed in recent years. Case 89 illustrates the importance of adequate laboratory evaluation before additional administration of P<sup>32</sup>, and the relatively increased sensitivity to this form of therapy reportedly observed in elderly patients.<sup>50</sup>

#### COMMENTS

Although other myelosuppressive forms of therapy have been suggested from time to time, 62, 63, 64, 65 P32 appears to be the agent of choice. 60, 67 This is because of its convenience and virtual lack of unpleasant side-effects, as well as its demonstrated efficacy. The advantages of this form of therapy over phlebotomy and hemolytic agents have been described. Our findings are in agreement with these opinions. However, we wish to emphasize, as others have, the importance of phlebotomy for rapid control while the marrow depression is being induced. Venesection may also be quite effective in mild cases, or as a temporary measure when P32 is not available. The long-term use of this procedure concomitant with a diet deficient in iron results in a hypochromic, microcytic polycythemia which may actually be reduced by the administration of iron. Furthermore, the need for frequent treatments renders this measure impractical for long-term control in many cases.

The danger that the incidence of leukemia may be increased in patients treated with P32 is at present very difficult to evaluate. Much depends upon the view that one takes about the etiology of the two diseases, which at present remains quite speculative. It would appear reasonable to assume that polycythemia belongs to the group of myeloproliferative disorders or perhaps, as Castle has suggested,68 that it might be merely a manifestation of leukemic process producing "competitive anoxia" within the marrow. The close interrelation of these two conditions is further emphasized by an occasional case where the reverse sequence of events is observed, i.e., polycythemia developing in a patient with chronic leukemia.57 If one accepts these interpretations it is evident that, at certain stages, the separations of myelofibrosis, granulocytic leukemia and polycythemia vera into distinct entities may be impossible. 69 Finally, it is generally agreed that the figures reported do not seem to indicate an increased incidence of leukemia other than might be reasonably explained by improving the survival to such an extent as to allow this stage of the disease to become manifest.

In conclusion, it is particularly important to appreciate that under proper control these patients are entirely capable of leading normal, productive lives without physical handicap. They should therefore be managed from this standpoint, and not be made invalids or encouraged to restrict their daily activities.

# SUMMARY

The course and treatment of 97 patients with polycythemia vera receiving radioactive phosphorus at this hospital for the last 10 years are reported. Of these, 28 have died, six (21%) with chronic granulocytic leukemia and two (7%) with myelofibrosis. It is difficult or even impossible to separate these three disorders, with present-day knowledge. Furthermore, it does not appear that P³² has increased the occurrence of leukemia over what may be expected with the improved survival. The median survival in the present series is 11 years from onset of symptoms, and the median age at death is 65 years. This is similar to Lawrence's experience, and represents an improvement over figures reported with therapeutic methods other than P³² administration.

Of 78 patients followed at regular intervals, 67 (86%) obtained successful remissions, defined as an absence of symptoms and erythrocyte counts of below 6,000,000 for over one year. The remaining 11 (14%) all derived some benefit and, of six who are still living, three are asymptomatic, and all have erythrocyte counts below 7.0 million. Leukocyte counts over 25,000, relatively long duration of the disease process at time of therapy, and particularly marked splenomegaly (over 10 cm.) were found to be of prognostic value in predicting a poorer response to P<sup>32</sup>.

## SUMMARIO IN INTERLINGUA

Es reportate le curso clinic de 97 patientes de polycythemia ver, insimul con lor tractamento con phosphoro radioactive al Hospitales del Universitate Wisconsin in le curso del passate 10 annos. Initialmente le therapia esseva supplementate per phlebotomia con le objectivo de reducer le numeration erythrocytic a infra 6.000.000. Le dose initial de P³² esseva individualisate secundo le pesos corporee e le numerationes erythrocytic del patientes. Illo variava inter 2,0 e 10,0 millicuries, con un valor medie de 6,0. Le droga esseva administrate per via oral, excepte in sex casos. In recente annos le tendentia ha devenite usar plus micre doses initial. Le patientes esseva re-examinate al clinica de visita a intervallos de inter tres e sex menses. Le stato del patients esseva considerate como ben regulate quando lor numeration erythrocytic non excedeva 6.000.000 e quando illes esseva asymptomatic. Si iste stato persisteva un anno o plus, il esseva concludite que le obtention de un remission habeva succedite.

Vinti-octo patientes moriva, sex (21%) con chronic leucemia granulocytic e duo (7%) con myelofibrosis. In le lumine del cognoscentias nunc disponibile, il non es possibile separar iste tres disordines. In plus, il non pare que P³², in meliorar le superviventia, ha augmentate le incidentia relative de leucemia. Le superviventia medie in le presente serie a partir del declaration del symptomas es 11 annos, le etate medie al tempore del morte es 65 annos. Isto es simile al resultatos obtenite per Lawrence e representa un avantia in comparation con le statisticas reportate pro methodos altere que P³².

Ex 78 patientes qui esseva re-examinate a intervallos regular, 67 (86%) obteneva remissiones successose. Le remanente 11 (14%) non esseva sin beneficio. Inter le sex qui vive ancora, tres es asymptomatic, e omnes ha numerationes erythrocytic de infra 7.000.000.

Le manifestationes toxic esseva restringite a excessive depressiones medullar e occurreva in tres del casos. Numerationes leucocytic de plus que 25.000, relativemente longe historias del processo pathologic al tempore del initiation del therapia, e—specialmente—marcate grados de splenomegalia (plus que 10 cm) se monstrava de importantia prognostic in tanto que illos faceva predicer un responsa pauco favorabile al therapia a P<sup>32</sup>. Il debe esser signalate que, si tosto que un adequate subjugation del morbo ha essite effectuate, le patiente es integremente qualificate a viver un vita normal e productive, sin ulle handicap physic.

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# TETRACYCLINE PROVOCATION IN LUPUS **ERYTHEMATOSUS\***

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Hypersensitivity is largely responsible for the unpredictability of lupus erythematosus (L. E.). The unwary physician, and even the wary one, may prescribe a necessary drug only to see devastation wreaked by a violent hypersensitivity reaction. Such a reaction may be the first intimation of the presence of L. E., it may herald accelerated systemic spread in discoid lupus, or it may be the final disastrous turn in the course of a patient with systemic lupus erythematosus. When such a reaction occurs, the physician's 20/20 hindsight is small comfort to him, and of little use to the patient. The purpose of this report is to provide some foresight by calling attention to what may be a hitherto unappreciated provocative potential of the tetracyclines in lupus erythematosus.

## CASE REPORTS

Case 1. A 63 year old woman was seen at her home on December 17, 1955, with fever and a sore throat which had the clinical appearance of streptococcal pharyngitis. She was given oxytetracycline. The same drug had been administered five months earlier by another physician for a respiratory infection, with results described as neither helpful nor harmful. The pharyngitis and fever subsided quickly, but four days later the patient broke out with generalized urticaria. Simultaneously, nasal obstruction, rhinorrhea, tinnitus, urinary frequency, tenesmus and a sense of pressure in the suprapubic region appeared. The urticaria cleared in a few days, but the other symptoms persisted in the ensuing weeks, during which the patient developed malaise and migratory arthralgias.

After several weeks of these symptoms she again had fever and sore throat, this time with left-sided pleuritic pain, but she did not consult a physician because of fear of being given an antibiotic. She then developed swelling and redness over the lateral malleolus of the left ankle. A consulting dermatologist felt that the lesion represented nodular vasculitis, but, with the possibility of a fixed drug eruption in mind, suggested a change from her bedtime hypnotic, secobarbital, to glutethimide (Doriden). The leg lesion did not improve, and in April the proximal interphalangeal joints of her fingers became swollen, tender and stiff. Shortly thereafter she developed a macular eruption over the upper trunk, arms, neck and head which became a confluent, fiery erythema. This was accompanied by fever, hoarseness, petechiae over the legs, and a grade 2 apical systolic murmur. At this time the

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sedimentation rate was 60 mm. per hour (Westergren), and the L. E. test was positive.

The patient had begun taking steroids six years prior to the present illness, at the suggestion of a radiologist who had found extensive osteoarthritis involving her cervical spine. In recent years she had taken hydrocortisone, 20 mg. daily, and this had been doubled with the appearance of urticaria in December. The reaction described above occurred while she was taking 40 mg. of hydrocortisone daily.

Prednisone in doses of 30 mg, daily was substituted on April 20, with no clearcut response. Vesicles appeared on the lips and oral mucosa, and fever continued. It was noted that her dermatitis was distinctly worse each morning. Glutethimide was stopped and improvement was prompt: fever, arthralgia and dermatitis subsided (with desquamation). The L. E. test was still strongly positive on May 17 (L. E. cells comprised 0.1% of the 1,000 leukocytes counted). Two months later it was negative, and prednisone dosage was gradually reduced to 20 mg. daily.

Intractable insomnia prompted a trial of glutethimide in August. The morning

Intractable insomnia prompted a trial of glutethimide in August. The morning after a single dose (1 gm.), vivid erythema covered the entire body, and arthralgia recurred in the fingers. This exacerbation responded within five days to increased doses of prednisone. Unfortunately, an L. E. cell test was not done during this brief flare-up.

L. E. tests in July and September, 1956, and October, 1957, have been negative. The sedimentation rate and blood counts have also remained normal, and all physical stigmata of her illness have disappeared.

Comment: It seems fairly certain that this patient developed systemic L. E. de novo following a hypersensitivity reaction to tetracycline. Despite her completely negative history for any other allergic reactions in the past, the tetracycline reaction did not represent an idiosyncrasy, but was a true sensitization phenomenon, since the drug had been administered without reaction five months earlier. This had served as the priming, or sensitizing, dose. Once the reaction occurred and active L. E. supervened, her reactivity was at exquisite pitch, as shown by the violent reactions to glutethimide, a drug of low sensitizing potential. Interestingly, the reactions to tetracycline began while she was taking hydrocortisone, and the reactions to glutethimide occurred while she was taking prednisone. Remission has thus far been complete (18 months).

Case 2. A 38 year old housewife developed joint pain, chills and fatigability after several days of swimming and sunning in July, 1953. During the next several weeks she noted mild fever, swelling of the hands and face, and a red, scaling eruption over her cheeks, nose and one side of the neck.

Her past history was significant in that she was of fair complexion, had red hair, and had always been prone to painful sunburns. She had had pneumonia at age 12 and at age 16. Measles and mumps had not occurred until she was an adult, and she stated that she had had "flu" eight times in succession in 1950.

Initial physical examination in November, 1953, showed generalized lymphadenopathy and an eruption typical of L. E. on the face, shoulders and arms. Laboratory studies showed 3.72 million erythrocytes per cubic millimeter; hemoglobin, 10.8 gm.%; leukocytes, 3,350. The sedimentation rate was 28 mm., serum proteins were normal (Howe), and the cephalin flocculation test was 4 plus at 24 hours. Urinalysis disclosed 1 plus albuminuria and 3 plus bacteria on the smear. An electrocardiogram and a chest roentgenogram were normal. The L. E. test was nega-

tive, but a clinical diagnosis of systemic L. E. was made, and the patient left the hospital taking chloroquine, 250 mg. twice daily. She was given an antihistaminic and oxytetracycline to control the severity of her frequent respiratory infections.

During the next two years she continued taking chloroquine and improved steadily. The dermatitis and arthritis disappeared, and she gradually resumed full household duties. Mild anemia persisted, but the urine was normal and the sedimentation rate gradually fell to 3 mm. per hour. Chloroquine dosage was gradually reduced, and was stopped in January, 1956.

Chloroquine therapy was withheld for only six weeks, during which time the patient developed joint pain and crops of pink macules on the face and arms. In late February severe joint pain, fever and malaise prompted resumption of the drug. She did not respond and was hospitalized in March. The L. E. test was strongly positive, the sedimentation rate was 36 mm. per hour, and anemia, leukopenia and albuminuria were again present. Improvement occurred with bed-rest, but was not maintained after discharge. For the first time the urine showed 4 plus albumin, hyaline and granular casts, erythrocytes and leukocytes. Prednisone, 20 mg. daily, was added to her regimen in June. Therapeutic abortion for an early pregnancy was performed in July, 1956. During the next eight months all skin lesions and arthralgia disappeared, she experienced considerable return of strength, and laboratory studies showed only minimal abnormalities.

Beginning in January, 1957, the urinary findings began to worsen despite continued clinical improvement. Considerable numbers of bacteria were found in multiple urine specimens, and in March tetracycline was prescribed.

Within 48 hours the patient developed fever, chills, severe nausea, facial edema, a fresh crop of nummular erythematous blotches distributed over the entire body, and aphonia. She stopped the tetracycline but resumed it a few days later at lower dosage. Fever and edema subsided, although the rash persisted. She discontinued the tetracycline in June, but the eruption had developed new components: generalized erythema and multiple superficial necroses which coalesced into extensive shallow weeping ulcerations on the arms and upper trunk (figure 1). She entered the hospital on July 2, 1957, and her temperature showed a steady rise, reaching 105° F. on the fourth day. L. E. smears were strongly positive, the sedimentation rate reached 61 mm. per hour, and anemia was severe (2.6 million erythrocytes and 7.2 gm. hemoglobin). The urine was loaded with all the formed elements, and the serum protein electrophoresis showed profound albumin deficiency (0.92 gm.%), with normal values for all the globulins. The patient died on the sixth day, and autopsy showed pathologic findings typical of systemic lupus erythematosus, and an agonal streptococcal septicemia.

Comment: In this patient, tetracycline had been used to good advantage early in the course of her disease to treat respiratory infections. A later attempt to employ the drug proved disastrous, setting off a violent reaction which appeared to hasten her death. While it could be argued that the deterioration of the urinary findings implied a gloomy outlook, it remains incluctably true that the cutaneous and systemic flare which followed tetracycline never subsided, but progressed until her spectacular exitus.

Case 3. A 51 year old mechanic was hospitalized in June, 1957, because of dyspnea, joint pain and night sweats. Two years earlier a mobile unit screening chest roentgenogram had shown diffuse pulmonary fibrosis. Subsequent serial films had shown no change. In May, 1956, he had developed pain and stiffness in the fingers and right shoulder. Within a few weeks there were fibrotic ankylosis of

the shoulder and bulbous "drumstick" enlargement of the fingertips. During the next several months the patient obtained little relief from a host of medications and physiotherapy. Following a rectal fistulectomy in March, 1957, he developed pain in all peripheral joints, fever, drenching night sweats, cough with mucoid expectoration, and progressive dyspnea.



Fig. 1. Case 2 at height of fulminant L. E. exacerbation following tetracycline. Edema and erythema were generalized, but coalescent ulceration did not involve the face or upper chest.

His past history was significant in that he had been rejected for military service in World War II because of a cardiac murmur. In 1949 he had been incapacitated with a "stroke," characterized by a right hemiparesis which lasted one day, and aphasia for six months.

Physical examination showed evidence of weight loss (14 pounds), clubbing of the fingers and toes, tenderness and stiffness of all peripheral joints, with moderate synovial thickening about the wrists and ankles, and fine moist and sibilant râles

scattered over both lung fields.

Laboratory studies showed an erythrocyte count of 4.2 million, a hemoglobin of 11.4 gm.%, and a leukocyte count of 13,900. The sedimentation rate was 107 mm. per hour. The serum albumin was 3.35 gm.%, globulin, 3.65, and electrophoretic analysis showed slight elevation of each globulin fraction, with no distinct preponderance. Normal results were obtained with the following studies: urinalysis, VDRL, fasting blood glucose, nonprotein nitrogen, serum calcium, alkaline phosphatase and skin tests with PPD first strength, coccidioidin 1:100, and histoplasmin. The electrocardiogram was normal, and the electro-encephalogram showed a generalized slow wave dysrhythmia. Roentgenograms of the skull, hands, feet, shoulders and urinary tract were normal. Chest films showed extensive fibrosis and many fine granular densities involving chiefly the lower lobes. Sputum culture showed only banal respiratory flora, with slight predominance of Micrococcus pyogenes. Bronchoscopy, bronchography and cytologic study of bronchial washings disclosed no evidence of intrabronchial disease.

After bronchoscopy the patient spiked temperatures to 103° F., and penicillin and tetracycline were administered. At this time one of the consultants suggested a search for L. E. cells, and they were found. Interpretation of this finding was left in abeyance.

Because of the extensive pulmonary fibrosis accompanied by painful arthropathy, the patient was started on steroid therapy (prednisone, 10 mg. four times daily).

Within one month he became free of pain and the L. E. test was negative.

Two months later he had regained his normal weight, had returned to work, and noted only mild exertional dyspnea. At this time tetracycline was administered provocatively, in doses of 2 gm. daily for one week. An L. E. test at the end of the week was strongly positive. Careful questioning and physical examination failed to uncover any symptoms or signs of an untoward reaction to the tetracycline.

The next examination, in January, 1958, showed that the patient had continued to improve and to gain weight. He had discontinued prednisone one week prior to examination, and the L. E. test was negative. Oral penicillin was administered provocatively, and after five days the L. E. test was strongly positive. Again, no untoward symptoms accompanied the change from a negative to a positive L. E. test.

Comment: This patient initially demonstrated positive L. E. tests while he was taking penicillin and tetracycline simultaneously. The tests reverted to negative when the antibiotics were stopped, and a positive test was later provoked by each antibiotic separately while he was receiving steroids.

It does not appear possible to decide at this stage of his illness whether this patient has systemic L. E., or pulmonary fibrosis with rheumatoid arthritis, as described by Caplan 1 and others.\*

#### DISCUSSION

The victim of lupus erythematosus has been described as "first and fore-most an allergic person, explosively and furiously responsive." An impressive aggregate of clinical, pathologic and experimental evidence indicates that the basic pathogenetic mechanism in L. E. involves an intense antigenantibody reaction. 3, 4, 5, 6 Prior to the advent of modern therapy, patients

<sup>\*</sup> A diagnosis of systemic L. E. was finally made in April 1958 when he developed acute pleuritis with a positive L. E. blood smear.

with L. E. had to be carefully shielded from the most trivial stress. Many instances were recorded where discoid lupus first made its appearance at the site of minor trauma, such as a cut, a burn, a tattoo or a tuberculin test. Furthermore, so-called dissemination of discoid lupus would occur after exposure to cold, sunlight and x-rays. Although present therapy, particularly with the newer steroids, has greatly improved the prognosis of patients with L. E., their proclivity to react unfavorably to drugs is apparently not influenced. In all three of our patients the hypersensitivity reaction occurred while steroids were being administered.

L. E. reactions may occur after physical stress and with an impressive number of drugs (table 1). While the evidence implicating certain of these drugs has perforce been circumstantial, the causal role of hydralazine would appear to be beyond doubt on two counts: (1) the incidence of the "hydralazine syndrome" is far higher than that ascribable to chance (8% of patients on long-term therapy with the drug); <sup>20</sup> and (2) the syndrome, complete with strongly positive L. E. tests, is reproducible in laboratory animals.<sup>25</sup>

TABLE 1
Agents Provocative in Lupus Erythematosus

,		*
Sunlight		Mesantoin 16
X-ray 9		Gold 8, 9, 12, 17
Trauma 10, 11		Phenylbutazone 18
Cold 9, 12		Prolonged steroid therapy 1
Horse serum <sup>3</sup>		Hydralazine 20, 21
Typhoid-paratyphoid vaccin	e 13	Antihistaminics 22
Tetanus antitoxin 14		Quinine 9
Streptococcus toxin 13		Bismuth *
Tuberculin 2,8		Sulfonamides 22,23
Hydantoin 14		Penicillin 14.15.24

The L. E. reactions which have occurred following various drugs may be categorized as:

1. Exacerbations of established L. E., either dissemination of discoid L. E., or ingravescence of systemic L. E.

2. De novo appearance of clinical syndromes indistinguishable from systemic L. E. with positive L. E. tests.

3. Positive L. E. test in the absence of signs or symptoms.

The first type of L. E. reaction terminated fatally in our second patient. The second type of reaction occurred in our first patient, and is what usually occurs in the hydralazine syndrome. In the third type of reaction, exemplified by our third patient, the question arises as to whether the patient actually has L. E. This decision hinges, in turn, on the specificity of the L. E. test.

Absolute specificity has been claimed for the L. E. test, <sup>26, 27, 28</sup> although positive tests have been described in a number of highly disparate conditions (table 2). Others <sup>7, 29</sup> have been content to attach diagnostic significance only to strongly positive L. E. tests. Even this stand is difficult to maintain in the face of the high incidence of positive L. E. tests in the hydralazine syndrome and rheumatoid arthritis (up to 27%).<sup>44</sup>

TABLE 2
Conditions in Which L. E. Cells Have Been Found

Pernicious anemia =
Hemolytic anemia **
Multiple myeloma 20, 31, 22
Leukemia 30
Thrombotic thrombocytopenic purpura 34
Viral hepatitis 86, 86, 37
Hepatic cirrhosis 35, 36
Tuberculosis 30, 38

Dermatitis herpetiformis <sup>20</sup> Senear-Usher pemphigus <sup>20</sup> Scleroderma <sup>20</sup> Periarteritis nodosa <sup>40</sup> Rheumatoid arthritis <sup>18, 22, 41, 42</sup> Amyloidosis <sup>20</sup> Normals <sup>42</sup>

Because of the difficulties in assigning specificity to a test with so many false-positives, some investigators have concluded that the L. E. phenomenon is simply a particular mode of reaction to various noxious substances. This view has gained recent support from the experimental work of Brunson,<sup>44</sup> who produced the pathologic changes characteristic of L. E. by means of a generalized Shwartzman's reaction. Most significantly, the pathologic changes of other collagen diseases could also be produced by the same means. It would appear that the L. E. phenomenon is only one (spectacular and relatively easy to identify) type of tissue reaction which may occur in patients with pathergic responsiveness.

From a practical standpoint, the hypersensitivity of patients with apparent or occult L. E. produces serious therapeutic pitfalls, epitomized in O'Leary's <sup>45</sup> statement that "unfortunately the deaths we encounter in the chronic discoid type (of L. E.) are usually the result of treatment." The incidence of L. E. is on the rise, not only because of sharpened facility in diagnosis provided by the L. E. test, <sup>25</sup> but also because of the wider use of therapeutic agents which are potent sensitizers. Occurrence of a drug reaction in any patient was suggested by Tumulty <sup>47</sup> as a signal to consider the possible presence of L. E. Our experience tends to confirm his observation that disastrous drug reactions in known or latent cases of L. E. can be avoided only if therapy is prescribed with the greatest circumspection.

It is worth emphasizing that steroids afforded our patients no appreciable protection against their L. E. reactions. This is consonant with recent reports of failure of the steroids to prevent various severe drug reactions, including anaphylaxis.<sup>48</sup>

#### SUMMARY

Three patients are described in whom L. E. reactions occurred after administration of tetracycline. These reactions, and L. E. reactions to other drugs, may take three forms:

- 1. De novo appearance of systemic L. E.
- 2. Exacerbation of known L. E.
- 3. Positive L. E. tests without clinical signs or symptoms of L. E. Circumvention of such reactions depends upon the physician's awareness of the sensitizing potential of the medications he employs, and vigilant conservatism in their use.

### SUMMARIO IN INTERLINGUA

Hypersensibilitate es responsabile in grande mesura pro le inpredicibilitate de lupus erythematose. Iste reporto signala lo que es possibilemente un previemente non recognoscite potential provocatori de tetracyclina in lupus erythematose.

Un femina de 63 annos de etate disveloppava urticaria, polyarthralgia, e dermatitis scarlatiniforme post therapia a tetracyclina pro pharyngitis streptococcal. Le test pro L.E. esseva positive. Un intense e prolongate curso de prednisona resultava in un remission que ha durate 18 menses.

Un femina de 38 annos de etate disveloppava classic L.E. systemic post forte exposition a lumine solar. Dermatitis, arthralgia, leucopenia, anemia, e sedimentation accelerate, omne iste symptomas se meliorava continuemente durante duo annos de therapia con reposo e chloroquina. Le administration de tetracyclina, interprendite pro bacteriuria, esseva sequite per un recidiva violente que se culminava in le morte del patiente.

Un mechanico de 51 annos de etate recipeva penicillina e tetracyclina pro un reaction febril post un investigation bronchoscopic de chronic fibrosis pulmonar associate con arthritis rheumatoide. Le test pro L.E. esseva positive quando le mentionate drogas esseva administrate, sed duo menses plus tarde illo esseva negative. Subsequentemente, positive tests pro L.E. esseva evocate repetitemente per administrationes de penicillina o de tetracyclina.

Reactiones de L.E. pote occurrer post stresses physic e post le administration de varie drogas. Le reactiones de L.E. pote esser categorisate sequentemente:

 Exacerbationes de establite lupus erythematose, i.e. dissemination de L.E. discoide o ingravescentia de L.E. systemic.

2. Le manifestation initial de syndromes clinic que es indistinguibile ab L.E. systemic e que es accompaniate de tests positive pro L.E.

3. Tests positive pro L.E. in le absentia de signos o symptomas.

Le specificitate del test pro L.E. es satis alte sed non absolute. Isto es evidente ab le occurrentia de tests false-positive in un numero de conditiones, particularmente in le syndrome a hydralazina e in arthritis rheumatoide.

Steroides non provide nostre patientes con grados appreciabile de protection contra lor reactiones de L.E. Le circumvention de tal reactiones depende de si o non le medico es conscie del potential sensibilisatori del medicationes que ille emplea e del vigilantia e del conservatismo con que ille se servi de illos.

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# **OUINIDINE PURPURA: REPORT OF SIX CASES\***

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Although Seyderhelm in 1927, in a very brief clinical discussion, associated thrombocytopenic purpura with quinidine administration, Broch 2 in 1941 was the first to give a detailed case report of this phenomenon, to speculate as to the mechanism of the thrombocytopenia, and to provide evidence that the thrombocytopenia was indeed due to an idiosyncrasy to quinidine. In the period from 1947 to 1955 numerous single case reports 3-23 and a report of two cases by Bigelow and Desforges 24 were published. Gold 25 also mentioned two cases of thrombocytopenia due to quinidine in a discussion of quinidine therapy. Nudelman et al.5 expressed the opinion that purpura due to quinidine was apparently extremely rare, in contrast to the occasional case of purpura associated with quinine administration. Norcross 7 described his case as a rare idiosyncrasy to quinidine. Larson 16 in 1953 reported a case of purpura and described it as a rare complication of quinidine therapy. With increasing recognition of quinidine purpura there have been more frequent case reports, and in 1956 two reports 26, 27 appeared, with series of five and six cases, respectively. Although purpura due to quinidine sensitivity is undoubtedly rare when the total number of patients receiving quinidine is considered. Bolton and Dameshek 26 state that quinidine now seems to be the most common cause of thrombocytopenia as a manifestation of hypersensitivity to chemical substances.

It is the object of this report to describe six cases of thrombocytopenia associated with quinidine administration observed at the University of Michigan Hospital and the Simpson Memorial Institute during a period of 50 months. The last four cases were seen during a period of 15 months.

#### CASE REPORTS

Case 1. A 68 year old woman was admitted to the hospital because of recurrent hemorrhagic lesions of mouth and skin. During the four years before admission she had been given quinidine intermittently for episodes of palpitation associated with slight shortness of breath. Two weeks prior to admission she developed severe epistaxis and "blood blisters" on her lips and in her mouth. These were followed by a fine red eruption over shoulders, abdomen and lower extremities. She consulted her physician, who gave her ascorbic acid and cortisone. The lesions cleared over a period of a few days. On the day before admission there was recurrence of hemor-

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rhagic lesions, with vesicles on the lips, vaginal bleeding, cutaneous bleeding and tarry stools. The patient did not remember whether she had taken quinidine immediately before the first episode of bleeding, but did recall that she had taken one tablet of quinidine two days before admission.

Physical examination revealed an adequately nourished elderly woman who was acutely ill. The blood pressure was 130/75 mm. Hg. The pulse was 110/min., and the temperature 100° F. Petechial lesions were present over the legs, abdomen and shoulders, with ecchymotic areas on the cheeks and lips and hemorrhagic lesions on the tongue, buccal mucous membranes and gingivae. There was crusted blood in the left nostril. A nodule was present in the right lobe of the thyroid. The heart was slightly enlarged to percussion, and there was an apical systolic murmur, blowing in character. The cardiac rhythm was irregular. Calf muscles were tender bilaterally, but Homans' sign was negative. The liver was palpable at the right costal margin; the spleen was not palpable. There were small bleeding points in the vaginal mucosa.

The electrocardiogram showed auricular fibrillation. X-ray examination of the heart revealed a localized aneurysm of the upper anterior portion of the left ventricle. Urinalysis was not remarkable. The stool guaiac test gave a 4 plus reaction.

The hemoglobin was 13.9 gm./100 ml.; hematocrit, 39%; red blood cell count, 4,800,000/cu. mm. The white blood cell count was 8,050/cu. mm., with 82% neutrophils, 2% large lymphocytes, 8% small lymphocytes, 7% monocytes and 1% eosinophils. There was slight anisocytosis of the red blood cells, and the platelets were greatly diminished on the blood film. Sternal marrow aspirate was normal except that the numerous megakaryocytes were without evidence of platelet release.

No quinidine was given after admission to the hospital. Active bleeding subsided within 24 hours, ecchymoses cleared, and the patient was discharged on the tenth hospital day. Platelet counts (indirect counts on dried stained films) are plotted in figure 1 according to day of hospitalization.

Platelet agglutination studies were done on plasma drawn on the seventh hospital day by the technic of Weisfuse et al.<sup>19</sup> The combination of platelet suspension, quinidine and the patient's plasma gave a 3 plus agglutination reaction. When isotonic saline was substituted for the quinidine solution in the system, no agglutination occurred. Controls with normal serum were also negative. It is worthy of note that this patient's plasma was kept frozen for a period of 45 months before the tests were done.

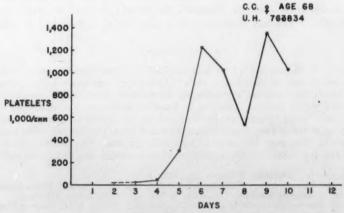


Fig. 1. Case 1. Platelet counts after admission to the hospital.

Case 2. A 66 year old woman was referred to the Simpson Memorial Institute because of recurrent attacks of purpura, occurring during the seven months prior to admission, and because of leukopenia.

Four years before admission the patient had had her first attack of cardiac palpitation associated with a sense of fullness and pounding in her throat. The attacks of palpitation recurred and became more frequent. Quinidine sulfate was prescribed for the cardiac disturbance three years before admission. She was advised to take one 0.2 gm. tablet every four hours on the day of the attack, three tablets on the day after the onset of palpitation, and then to stop the drug.

Seven months prior to admission the patient had noted the onset of recurrent purpura. The episodes of purpura were always associated with the attacks of palpitation, and would usually occur on the second day of the attack, preceded by chills the night before. The bleeding consisted of epistaxis, petechiae and ecchymoses of skin and oral mucous membranes. The hemorrhagic lesions would clear completely, only to recur with the next episode of palpitation.

Over a 10-year period, beginning approximately 17 years prior to admission, this patient had had migratory symptoms involving the proximal interphalangeal joints of the fingers and other small joints. The symptoms consisted of pain and stiffness.

Because of an elevated basal metabolic rate, she was given propylthiouracil for a period of nine months, beginning 21 months before admission.

Physical examination revealed a moderately obese woman in no distress. The blood pressure was 120/65 mm. Hg. There were resolving petechiae over both lower extremities and the mucosa of the palate. The thyroid was not enlarged. There was no lymph node enlargement. The chest was normal. The left border of cardiac dullness was in the anterior axillary line. There was a harsh systolic murmur, loudest at the apex. There was an occasional premature systole. The liver was palpable 3 cm. below the right costal margin and the spleen 3 cm. below the left costal margin, at rest. There were Heberden's nodes over the distal interphalangeal joints of the fingers and limitation of motion of proximal interphalangeal joints. There was slight swelling of the right knee, and free fluid could be demonstrated in this joint.

The hemoglobin was 12.9 gm./100 ml.; hematocrit, 40%; red blood cell count, 4,500,000/cu. mm.; white blood cell count, 3,350/cu. mm. The differential count showed 60% neutrophils, 29% lymphocytes, 8% monocytes, 1% eosinophils and 2% basophils. There was slight anisocytosis of the red blood cells. Platelets appeared to be normal on the blood film. Sternal marrow aspirate revealed moderate erythrocytic hyperplasia. Megakaryocytes were increased in number and actively shedding platelets.

While this patient was in the hospital she was given 0.2 gm. quinidine sulfate by mouth. Platelet counts before and after this test dose, by the direct counting technic of Brecher and Cronkite, 28 are shown in figure 2. Two or three hours after administration of the quinidine there was onset of irritability and aerophagy. She had an aching sensation which began in her feet and ascended to involve the legs, back and head. The Rumpel-Leede test of capillary fragility became strongly positive, and the bleeding time (Duke) was longer than 20 minutes, four hours after quinidine. The temperature rose to a peak of 101.2° F. seven hours after the quinidine administration. There was no spontaneous bleeding with this episode.

It was concluded that the recurrent episodes of purpura were due to an idiosyncrasy to quinidine, and that the arthritis, splenomegaly and leukopenia constituted Felty's syndrome. The patient was advised not to take quinidine, and instead was given procaine amide hydrochloride for her palpitation. When she was seen three years later no further episodes of purpura had occurred. Platelet agglutination studies were negative at this time.

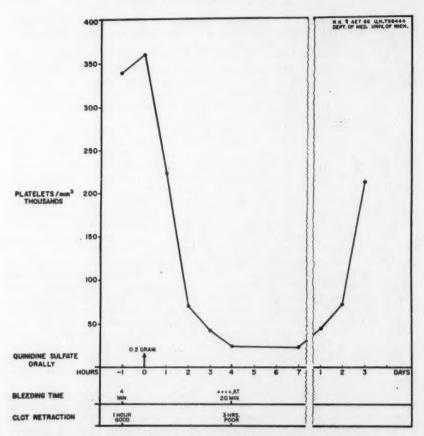


Fig. 2. Case 2. Platelet counts before and after the oral administration of 0.2 gm. quinidine sulfate.

Case 3. A 69 year old woman was admitted to the hospital because of a three-day history of easy bruising and other hemorrhagic manifestations. Eleven years prior to admission, at a time of emotional stress, she had first noted palpitation of her heart. She was also found to be hypertensive at that time. For five years previous to admission she had been given reserpine, one tablet twice daily, for her hypertension.

Three weeks before admission, after an electrocardiogram was done, the patient's physician had prescribed quinidine sulfate in a dosage of 0.2 gm. four times daily for two days, then twice daily. Three days before admission she noted blue areas on the trunk and arms. The next day small hemorrhagic lesions appeared on both lower extremities below the knees. The day before admission extreme ease of bruising was noted, and hemorrhagic lesions appeared on the tongue. The quinidine was discontinued that evening. On the day of admission minimal nasal bleeding was noted.

There was no history of allergy in the patient or her family. She denied the use of proprietary medications. She had had some exposure to household insecticides.

Physical examination revealed a moderately obese woman in no distress. The blood pressure was 180/96 mm. Hg. The pulse was 78/min. and regular. There were ecchymoses over both arms, the shoulders, the anterior abdominal wall and the lateral aspect of the right thigh. Smaller hemorrhagic lesions were noted on the tongue, gingivae, buccal and nasal mucosa, conjunctiva of the right eye and especially over the legs below the knees. The liver and spleen were not palpable. There was no lymphadenopathy.

The electrocardiogram was within normal limits. The chest film showed no

cardiac enlargement. The urine was not remarkable.

The hemoglobin was 12.7 gm./100 ml.; hematocrit, 42%; red blood cell count, 4,300,000/cu. mm.; white blood cell count, 6,550/cu. mm. The platelet count (indirect count on dried stained film) was 8,600/cu. mm. The differential count showed 54% neutrophils, 8% large lymphocytes, 19% small lymphocytes, 11% monocytes, 6% eosinophils and 2% basophils. There were slight anisocytosis and hypochromasis of the red blood cells on the film. Sternal marrow aspirate showed an increased number of megakaryocytes without evidence of platelet formation. Erythropoiesis and granulopoiesis were orderly. There was an increased number of eosinophils.

The Rumpel-Leede test of capillary fragility was positive. The clotting time

was seven minutes.

Reserpine was continued during hospitalization, but no more quinidine was given. Platelet counts after admission to the hospital are shown in figure 3. The hemorrhagic lesions gradually cleared, and the patient was discharged from the hospital on the eleventh hospital day. No testing in vitro or in vivo was done to

verify the diagnosis of quinidine purpura in this patient.

Case 4. A 53 year old woman was admitted to University Hospital because of recurrent bleeding from skin and mucous membranes. She had been followed at University Hospital for several years with diagnoses of hypertension, organic heart disease and paroxysmal auricular fibrillation. Because of symptoms of congestive heart failure, digitalis had been prescribed for her five years before admission. She was taking digitalis daily at the time of admission. Reserpine, in a dose of 0.50 to 1.00 mg. per day, had been given continuously for two years. Quinidine sulfate had been prescribed by her physician for the paroxysms of fibrillation, and this medication had been taken intermittently.

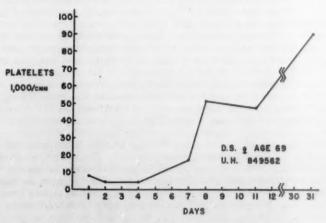


Fig. 3. Case 3. Platelet counts after admission to the hospital.

One month before admission she had had the sudden onset of hematemesis, melena and generalized purpura, including mucous membrane bleeding. This episode of bleeding ceased and the purpura subsided over a period of a few days without treatment. She had then been well up to the day before admission, when she had had the sudden onset of chills, back pain and headache. Several hours later she again developed hematemesis, melena and generalized purpura with "blood blisters" in her mouth.

The patient had quinidine in her home which had been prescribed for the paroxysmal auricular fibrillation. However, even with repeated questioning, she

denied having taken any quinidine during the previous two months.

Physical examination revealed an obese woman in mild distress. The blood pressure was 150/90 mm. Hg. The pulse was 92/min. and regular. There were petechiae and small ecchymoses over the entire skin area. Petechiae and hemorrhagic vesicles were present on the buccal mucosa, palate, pharynx and tongue. There was no lymphadenopathy. The chest was clear. The heart was at the upper limit of normal size on percussion. The heart sounds were normal. The liver and spleen were not palpable. There were mild hypertrophic changes in the joints of the fingers.

The electrocardiogram showed digitalis effects but otherwise was not abnormal. The chest film showed no abnormality. Urinalysis was normal. The stool guaiac test gave a 4 plus reaction. The "prothrombin" concentration (Quick) was 100%

of normal.

The hemoglobin was 12.2 gm./100 ml., and the hematocrit was 38%. The white blood cell count was 6,750/cu. mm., with a differential count of 59% neutrophils, 32% small lymphocytes and 9% monocytes. There was moderate toxic granulation of the neutrophils. The platelets were practically absent from the blood film. Sternal marrow aspirate was not remarkable except that megakaryocytes, present in normal numbers, showed no evidence of platelet release.

When the patient was admitted to the hospital the reserpine was stopped and the digitalis was continued. Without specific treatment for thrombocytopenia the bleeding ceased, and three days after admission the platelet number appeared to be

normal on the blood film.

Because the patient had denied recent ingestion of quinidine it was decided to administer 0.2 gm. quinidine sulfate by mouth while she was hospitalized so that the response could be followed carefully. Three hours after the quinidine had been given she experienced headache, backache and chills, and the temperature rose to 100.6° F. She had abdominal cramps and vomited. Intermittent vomiting continued for twelve hours. Four and one-half hours after the quinidine administration the bleeding time (Duke) was longer than 20 minutes and the Rumpel-Leede test was moderately positive. Within 12 hours of taking quinidine the patient developed widespread purpura involving both skin and mucous membranes. Within 24 hours she developed melena. The day after the quinidine administration she was given 500 ml. of fresh whole blood with siliconized apparatus, and treatment with ACTH, 25 units intramuscularly every six hours, was begun. The ACTH was continued for a period of five days.

No new hemorrhagic lesions appeared later than 24 hours after the quinidine administration, and the ecchymoses gradually cleared. The patient recovered without sequelae. Direct platelet counts during this episode are shown in figure 4. Because of the remote possibility that reserpine might have caused some of the hemorrhagic manifestations, the patient was also given reserpine after the platelet count had returned to normal. No symptoms and no thrombocytopenia resulted from the reserpine

administration

Plasma obtained from this patient after she had recovered from her thrombo-

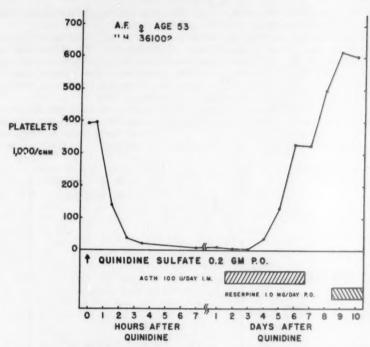


Fig. 4. Case 4. Platelet counts before and after the oral administration of 0.2 gm. quinidine sulfate. Note that reserpine was re-administered with no effect on the platelet count.

cytopenia was tested for platelet agglutinins. There was 2 plus agglutination of the platelet suspension in the presence of quinidine and the patient's plasma. When quinidine was replaced with saline in the system no platelet agglutination occurred.

Case 5. A 50 year old housewife was referred to the Simpson Memorial Institute because of recurrent purpura. She had taken quinidine intermittently for several years for "extrasystoles." She would take one tablet (0.2 gm.) of quinidine sulfate three or four times daily as necessary to control her symptoms. Because of other symptoms attributed to an anxiety neurosis, she had been given meprobamate, phenobarbital and Premarin.

Four months before admission the patient had had the sudden onset of bruising of the upper and lower extremities, bleeding of nose and throat, and conjunctival bleeding. She had also noted blood in her urine. Her physician prescribed cortisone and the bleeding ceased. She had two similar episodes of bleeding three months and one month before admission. At the time of the last episode her physician instituted prednisone therapy, and she was taking prednisone, 10 mg. daily, at the time of admission.

The patient could not correlate her hemorrhagic episodes with the ingestion of any medication, including quinidine. There was no personal history of allergy.

Physical examination revealed a well-appearing woman in no distress. The blood pressure was 180/110 mm. Hg. The pulse was 60/min. and regular. The skin and mucous membranes were free of hemorrhagic lesions. The remainder of the physical examination was within normal limits.

Urinalysis showed no abnormality. The chest film was within normal limits.

"Prothrombin" concentration (Quick) was 100% of normal.

The hemoglobin was 12.9 gm./100 ml.; hematocrit, 43%; red blood cell count, 4,700,000/cu. mm.; white blood cell count, 13,250/cu. mm. The differential count gave 83% neutrophils, 6% large lymphocytes, 6% small lymphocytes and 5% monocytes. The red blood cells showed slight anisocytosis. The platelet count was 330,000/cu. mm. The bleeding time (Duke) was 12 minutes, the clotting time (Lee-White) 8 minutes. The clot retraction was good in one hour.

Soon after the patient was admitted to the hospital prednisone was discontinued. An attempt was made to demonstrate inhibition of clot retraction by the addition of quinidine to the patient's blood. This was done with the technic of Macfarlane <sup>29</sup> as modified by Freedman et al.<sup>27</sup> No inhibition of clot retraction was demonstrated.

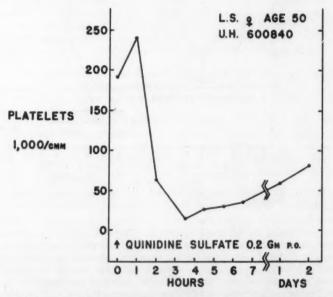


Fig. 5. Case 5. Platelet counts before and after the oral administration of 0.2 gm. quinidine sulfate.

In view of the negative test for inhibition of clot retraction it was thought that quinidine should be administered under observation. Accordingly, 0.2 gm. quinidine sulfate was given by mouth. No prednisone had been given on the two days prior to quinidine administration. No hemorrhagic phenomena resulted. There was a fall in the direct platelet counts, as illustrated in figure 5. The bleeding time (Duke), done five and one-half hours after quinidine administration, was 17 minutes. The temperature rose to 100.4° F. six hours after quinidine.

The patient was advised to take no more quinidine. No further episodes of

purpura have been reported.

Case 6. A 38 year old housewife was referred to University Hospital because of two episodes of bleeding, the first three months, the second three weeks previously. The first episode had been preceded by the taking of a tablet for palpitation. She had been taking the same medication intermittently for several years and thought it

was phenobarbital. Three hours after ingestion of the tablet she noted chilliness, fever and epistaxis. She then developed a pinpoint red rash over her body, most severe on the arms and legs. She was treated with blood transfusions and antibiotics. The symptoms cleared over a three-day period.

The second episode of purpura was very similar to the first except that the bleeding tendency was more severe, and ecchymoses were more prominent and persisted longer.

The patient denied any knowledge of quinidine ingestion at the time of her University Hospital examination. Communication with her physician revealed that the drug in question was quinidine. He also reported that thrombocytopenia had accompanied episodes of purpura.

Physical examination revealed an obese woman in no distress. The blood pressure was 155/90 mg. Hg. The pulse was 76/min, and regular. There was no evidence of active bleeding at this time. A resolving ecchymosis was present on the left anterior abdominal wall. The heart was not enlarged. There was a soft apical systolic murmur. The liver and spleen were not palpable.

The electrocardiogram showed no abnormality. The chest film was normal. The fasting blood sugar was 135 mg./100 ml., and a glucose tolerance test revealed a diabetic-type curve.

The hemoglobin was 12.5 gm./100 ml.; hematocrit, 41%; red blood cell count, 4,900,000/cu. mm. The white blood cell count was 9,250/cu. mm., with 58% neutrophils, 21% large lymphocytes, 14% small lymphocytes, 5% monocytes and 2% eosinophils. There was slight anisocytosis of the red blood cells. The platelets appeared to be normal in number on the stained blood film.

Plasma obtained 22 days after the most recent ingestion of quinidine gave 2 plus agglutination of platelets in the presence of quinidine. Controls showed no agglutination.

#### DISCUSSION

The most recent reports of Bolton and Dameshek,<sup>26</sup> Bolton <sup>30</sup> and Freedman et al.,<sup>27</sup> as well as earlier reports, have discussed adequately the mechanism of the thrombocytopenia in quinidine purpura. In the sensitive individual the quinidine-platelet combination forms an antigen against which a plasma factor is produced. With the combination of all three substances—platelets, quinidine and antibody—platelets are removed from the circulation and thrombocytopenia results.

The increasing frequency of case reports of this idiosyncrasy is illustrated in figure 6, where the cases previously reported are tabulated according to the year reported. Two deaths have been attributed to quinidine purpura. The total number of cases reported, where there is at least a good temporal relation of quinidine administration to the onset of purpura, including the cases of this report, is now 47. In 44 of these, data with respect to age and sex are given. Of these 44 cases, 36 are females and eight are males. Bolton and Dameshek have emphasized the higher incidence in females. The previously reported cases are plotted according to age in figure 7. As might be expected, the incidence of this form of purpura is higher in the older age groups, where quinidine is used more frequently. It is to be emphasized that thrombocytopenic

purpura due to an idiosyncrasy to quinidine should not be considered to be a rare phenomenon.

The recognition of quinidine purpura depends upon consideration of this agent as the cause of the purpura. If there is a history of quinidine administration previous to the onset of the purpura, and at times even without this history (case 4), especially in cases of fulminant purpura of abrupt onset, appropriate in vitro tests should be done to demonstrate platelet agglutination or decreased platelet function in the presence of quinidine. Agglutination may be demonstrated according to the technic of Weisfuse et al., or inhibition of clot retraction may be shown by the technic of Macfarlane of Macfarlane as adapted by Larson and Freedman et al.

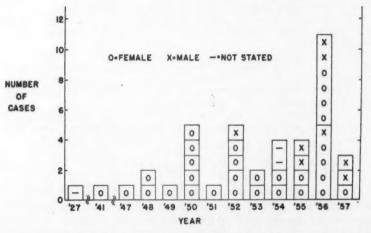


Fig. 6. Cases of quinidine purpura plotted according to year reported. Cases included in an individual report are grouped together. Note that most of these are single case reports. Total of 41 cases.

Sensitivity to quinidine may be detected in some instances by patch tests <sup>27</sup> and by intracutaneous tests. <sup>22</sup> However, the latter two tests may not be related to the thrombocytopenic effects.

If the in vitro studies do not demonstrate an abnormal factor in the patient's plasma, and quinidine is strongly suspected as the etiology of the purpura, it may be well to give the patient a small dose of quinidine, under close observation, to see the response with respect both to thrombocytopenia and to the clinical manifestations. After our experience with the in vivo test in case 4, it should be strongly recommended that re-administration of quinidine be done only as a final arbiter and in the presence of negative in vitro tests. The administration of the drug under these conditions can be justified, since it would be better to give the drug under

observation and prove the idiosyncrasy than to leave some doubt of the diagnosis and allow the drug to be tried under less favorable circumstances in the future. If a definite diagnosis of quinidine purpura is made, quinidine should never again be administered to the patient, since the result might well be serious or fatal hemorrhage.<sup>25, 81</sup>

The most important aspect of treatment of quinidine purpura is the removal of quinidine from the patient's medications. ACTH and corticosteroids may be beneficial in treatment of the purpura, but their value is open to question. Although ACTH was given in case 4, it is doubtful that the return of the platelets was thereby hastened. Platelet transfu-

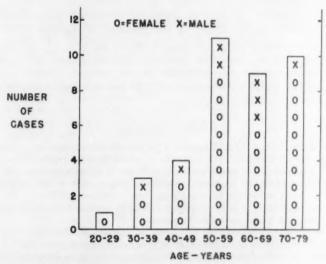


Fig. 7. Previously reported cases of quinidine purpura plotted according to age. Total of 38 cases.

sions would appear to be of limited value, since the agglutination resulting from this idiosyncrasy is due to a panagglutinin for human platelets. As Bolton and Dameshek have pointed out, quinidine is rapidly eliminated from the plasma. When such occurs, the platelet count will rise sharply and will usually reach normal levels in seven days.

As quinidine purpura becomes more widely recognized, it may be that a considerable number of cases may be removed from the classification of idiopathic thrombocytopenic purpura. It is also to be expected that the list of drugs and chemicals known to cause thrombocytopenia will be lengthened.

#### SUMMARY

- 1. Six cases of quinidine purpura were seen during a period of 50 months.
  - 2. All six patients were females; ages ranged from 38 to 69 years.
- 3. Five of the six patients received intermittent quinidine therapy for paroxysmal cardiac arrhythmias. One patient received a single course of quinidine treatment of three weeks' duration.
- 4. Quinidine purpura is not rare, and this diagnosis should be considered in all cases of fulminating bleeding.
- 5. In cases of suspected quinidine purpura, platelet agglutination tests or other appropriate in vitro studies should be done in an attempt to verify the diagnosis.
- 6. A diagnostic test dose of quinidine should be given to suspected cases of quinidine purpura only in the presence of negative in vitro tests and with due consideration for the risk to the patient.
- 7. Treatment of quinidine purpura consists primarily of avoiding further administration of quinidine to the patient. Supportive measures, including blood transfusions, ACTH and corticosteroids, should be used as the clinical situation dictates.

#### SUMMARIO IN INTERLINGUA

Ben que Seyderhelm in 1927 associava purpura thrombocytopenic con administration de quinidina, Broch in 1941 publicava le prime detaliate reporto de un caso de purpura per quinidina e le prime demonstration que le thrombocytopenia de tal casos esseva le resultato de un reaction idiosyncratic a quinidina. Plure autores in lor reportos de casos individual ha considerate iste disordine como rar. Plus recente reportos ha signalate que purpura per quinidina es probabailemente un occurrentia plus frequente que lo que on habeva supponite.

Le presente reporto concerne sex casos de purpura thrombocytopenic associate con le administration de quinidina. Omne le patientes esseva femininas. Lor etates variava inter 38 e 69 annos. Cinque de illas habeva recipite un intermittente therapia a quinidina in le tractamento de paroxysmal arrhythmias cardiac. Le sexte habeva recipite un sol curso de quinidina con un duration de tres septimanas. Le constatationes in le sanguine peripheric e in le medulla ossee esseva identic con illos de didiopathic purpura thrombocytopenic. Le idiosyncrasia relative a quinidina esseva demonstrate in cinque del casos per le reproduction de thrombocytopenia per medio del administration de un dose experimental de quinidina o per le demonstration de agglutininas plachettal in le presentia de quinidina per medio del technica de Weisfuse.

Es sublineate le facto que doses experimental de quinidina non debe esser administrate a patientes suspecte de suffrer de purpura per quinidina, excepte si tests in vitro pro agglutininas plachettal in le presentia de quinidina es negative. Tamen, quando le tests pro agglutininas plachettal es negative, il es probabilemente justificate administrar un dose experimental de quinidina, providite que le patiente es tenite sub observation, de maniera que su responsa con respecto a thrombocytopenia e su manifestationes clinic pote esser observate. Assi le diagnose de purpura per quinidina pote esser verificate o excludite.

Le tractamento de purpura per quinidina consiste primarimente de evitar omne administration additional de quinidina al patiente in question. Le quinidina in le

circulation es eliminate rapidemente, e usualmente le numeration del plachettas se restaura al norma intra septe dies. In certe casos, le uso de ACTH, de corticosteroides, e de transfusiones de sanguine es utile como mesuras supportative.

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# THE RATIONAL APPROACH IN THE USE OF BRONCHODILATORS IN CHRONIC RESPIRATORY DISEASE\*

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Pharmacologic bronchodilators have been used perhaps as long as any known medicinal agent. The use of ephedrine (ma hwang) is shrouded in the mists of Chinese antiquity. The burning of stramonium leaves appears at least as early as the 17th Century in Western Europe. Thus, sympatheticomimetic substances and parasympathetic paralysants appear early in the treatment of "bronchospastic" disease. Today many different compounds are available to be used as bronchodilators. These fall largely into three groups:

- 1. Epinephrine and related compounds.
- 2. Derivatives of scopolamine or hyoscyamine.
- 3. Aminophylline and other related substances.

The route of administration, choice of drug, dosage and anticipated result are among the problems that concern us here. These can best be understood by the physiologic aspects of disease in which they are used. Other aspects of the treatment of narrowed bronchi must be considered, including certain agents which indirectly influence bronchial caliber. Although these are not bronchodilators per se, discussion of their action is necessary to understand the over-all management of patients requiring bronchodilator therapy.

#### THE MEANING OF "BRONCHOSPASTIC" DISEASE

For many years the presence of a wheeze in expiration has been recognized as evidence of bronchial obstruction. Except where a localized cause (such as foreign body or tumor) can be identified, it is generally accepted as due to bronchospasm. Thus most physicians identify generalized wheezing with spasmodic asthma. This focuses the attention upon only one facet of bronchial narrowing in expiration. True spasm is more important in the young patient with acute asthma on an allergic basis than it is in

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"chronic asthmatic bronchitis" in the middle aged and elderly, but it is by no means the whole picture, even of the acute allergic episode in the young.

Often the young severe asthmatic develops a marked hypertrophy of the bronchial musculature which may be seen at autopsy. Usually he will respond to a parenteral or oral bronchodilator. Yet there is still a very important element of bronchial mucosal edema and of viscid obstructive secretions that cannot be neglected. In contrast, the elderly "asthmatic bronchitic" does not commonly develop hypertrophy of the bronchial musculature; at autopsy it may appear relatively atrophic. More significant are pathologic changes in the mucosa with patches of thickening and desquamation, eosinophilic infiltration, edema and the presence of many plugs of viscid secretions. In addition, permanent changes of lung recoil typical of emphysema can be demonstrated.1 There is, furthermore, a group of cases in whom apparently there is no thickening of the mucosa, no spasm of muscle, and no abnormal secretions, yet who wheeze in expiration and who complain of dyspnea. This is typical of senile emphysema. Therefore, in all cases with apparent "bronchospasm" there are other phenomena that require consideration.

It is not surprising, then, that measures aimed at relieving bronchospasm alone do not provide the full answer, even in those cases in whom it may be a relatively predominant factor. Our therapeutic approach, using pharmacologic bronchodilators, must be evaluated in terms of route of administration, considering possible effects on the mucosa and secreting surfaces, rather than purely in terms of muscular relaxation. Problems of epinephrine-fastness in the young asthmatic, the relatively minor response to parenteral bronchodilators in the asthmatic bronchitic, and the negligible response to bronchodilators seen in the senile emphysema group become more understandable. We cannot be surprised or dismayed when a patient fails to respond to a bronchodilator agent administered in such a way that it will largely affect only the bronchial musculature.

### THE PHYSIOLOGIC MECHANISMS INVOLVED IN EXPIRATORY WHEEZING

In the last five years there has been a marked change in our understanding of the mechanisms involved in expiratory wheeze. Originally Lander and Davidson 2,3 in 1938 studied the effect of the negative pleural pressure upon bronchial diameter. These investigators showed that where the pressure in the pleura was directly translated to the outside wall of bronchi, particularly if that pressure became more negative than normal, bronchi would be dilated. They further demonstrated that, in the presence of a diminution of the intrapleural pressure, as in pneumothorax, the bronchi would become much smaller than normal, even in full inspiration. Thus it became apparent that bronchial bore was in part a function of the gradient between air at atmospheric pressure inside the bronchi and the less-than-atmospheric pressure exerted upon the outer wall of bronchi by the recoil

tension of the lung. This can be measured to a large extent by the negativity of the intrapleural pressure.

The immediate application of these observations was more to the study of bronchiectasis than to the study of expiratory wheezing. However, Dayman in 1951 applied these concepts to patients with emphysema. He correlated the narrowed lumen of the smaller bronchi in full inspiration with the diminished lung tension and thus the diminished pressure gradient across the wall of small bronchi. He postulated that, as the pressure in the pleural cavity became positive in forced expiration in an effort to squeeze air out of recoilless lungs, bronchi became compressed, thereby preventing the flow of air from the lungs. The term given to this is "leakage flow." He applied this principle to the problem of expectorating secretions, show-

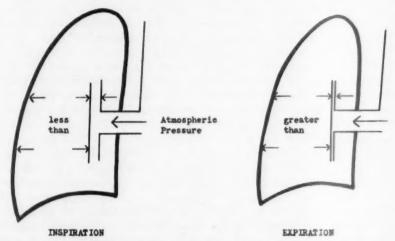


Fig. 1. Diagram of pressure relations of emphysematous lung.

ing that in such a situation cough must become ineffectual. Further work <sup>5, 6</sup> has done much to amplify this view of the nature of expiratory wheezing, using studies of pressure, air flow and cinefluorography. On quiet expiration a patient with emphysema does not wheeze. Any attempt to accelerate expiratory air flow produces the typical wheeze of forced expiration (figure 1). This occurs on effort, with cough or, in the very severe case, may be present at rest.

It is now clear that bronchial compression in expiration is an important mechanism in the production of wheezing, and that the effect of this will be markedly reinforced if there is further narrowing of the intrabronchial lumen by mucosal edema or by viscid secretions (figure 2). Under such circumstances, compression of the bronchi in expiration will develop sooner in forced expiration as the relatively high expiratory velocities demanded

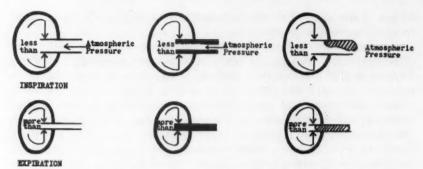


Fig. 2. Effect of mucosal edema or viscid secretions on bronchial bore in expiration.

by exercise or by cough are developed, with correspondingly strongly positive intrapleural pressures developing. Further bronchospasm or increased bronchial tonus will contribute to a narrowing of the bronchial lumen. However, the relative importance of muscular tonus as a mechanism contributing to obstructive wheezing can be seen to vary from patient to patient, and other important factors, such as reduced lung tensions, mucosal edema, retained secretions and uneven overdistention, starts to take its place in the over-all causation of expiratory wheezing. It becomes understandable that a patient with cystic disease of the lung (giant bullous emphysema), which acts as a space-occupying lesion and permits normal lung tissue to recoil and become grossly deflated, will wheeze on expiration. Not only does the cyst itself have poor recoil, but the remaining lung at its deflated volume is also affected. In such a patient, wheezing may totally disappear after excision or deflation of the cyst:7 The well known phenomenon that certain patients with epinephrine-fast spasmodic asthma previously responding to epinephrine may sometimes be improved by bronchoscopy with the removal perhaps of a bronchial cast becomes better explained. Perhaps most important of all, a rational approach to bronchodilator therapy becomes possible.

#### THE EPINEPHRINE-LIKE SUBSTANCES

These substances are of three types: the derivatives of epinephrine, the derivatives of amphetamine, and the derivatives of ephedrine. Each of these substances has a sympathomimetic effect, paralyzing smooth muscle in certain sites of the body but also producing various side-effects, particularly upon the vasculature and upon the heart itself. Ephedrine, longest in use, by and large has been used orally. It has a fairly profound vasoconstrictor effect, and at the same time a considerable amount of rebound hyperemia following vasoconstriction. Taken systemically, its effect appears to be less marked upon blood pressure and heart rate than are those produced by substances in the epinephrine series. Its psychic stimulant effect appears to be readily counteracted by the co-administration of a

barbiturate. Other derivatives—of which phenylpropanolamine (Propadine) is perhaps the best known—may produce less psychic stimulation. These substances, usually administered orally, are widely used to relax bronchial muscle. By injection they may produce some rise of vascular resistance and affect the blood pressure. Thus the place of ephedrine and related compounds in our armamentarium is as a basal bronchial muscle relaxant. The chief problem is the development of tolerance, which is relatively slow in appearance and seems to be uniform throughout the action of the drug. Therefore, the dosage can be increased. This group remains one of our most useful groups of systemic maintenance drugs for the treatment of bronchospasm.

Epinephrine, norepinephrine and other substances in the series are used both systemically and by nebulization. The use of epinephrine by injection in patients with acute spasmodic asthma is common practice. More recently, isopropylnorepinephrine (Isuprel) has been used as a sublingual The dose needed in the majority of cases is sufficient to produce definite cardiac acceleration and rise of blood pressure, and, with repetition, goose-pimpling and skin lividity. Administered by the systemic route, the main effect on the bronchi appears to be on the musculature, although there may be some effect on the mucosa! edema and on secretion. Many patients fail to respond to these drugs during an exacerbation of wheezing. Commonly, dosage is increased in the presence of failure of response, which results in a marked increase of the symptoms and signs of systemic toxicity, and a disappointing therapeutic response. For this reason there is a general change of viewpoint in the use of epinephrine and epinephrine-like substances away from the application systemically to the nebulized mode of administration.

Epinephrine and norepinephrine produce an intense vasoconstriction when applied locally. The amount of rebound hyperemia seen is not so great as with some of the other members of the series. The antisecretory effect appears to be less than the vasoconstriction. Administered by nebulizer, there appears to be some relaxation of the bronchomusculature. Because of the vasoconstrictor effect, relatively large doses may be given with little or no systemic toxicity. Therefore the view is gaining strength that these substances are best used by nebulization in patients with wheezing. The tolerated administered dose of racemic epinephrine (Vaponefrin), distributed at 3  $\mu$ -particle size by nebulizer, appears to be approximately 2.5 to 10 mg., as compared to a maximal tolerated dosage intramuscularly of 1 mg. The effect is seen at the site where the process that we wish to treat exists, and systemic toxicity usually is negligible. Even in patients with severe hypertension the administration of epinephrine by this route is not harmful, whereas administration parenterally may be open to criticism. Furthermore, it is more convenient to administer this group of substances by nebulizer than it is parenterally or orally. A patient can carry a hand

nebulizer. As his wheezing increases, or as he is about to undergo physical effort which would exacerbate his wheezing, he can treat himself with 6 to 12 "squirts" of his "hand gun," inspiring deeply each time. The effect of this is at least as great as the effect of a parenteral or oral administration of one of this group of substances, although it may not persist so long. This disadvantage is more than compensated for by the lowered toxicity, which permits more frequent use. We have found serious signs of overdosage to be relatively uncommon. In these patients mild insomnia, irritability and similar symptoms usually precede a rise in blood pressure. In the presence of such symptomatology one can advise the patient to lessen the dose, and also to use a long-acting barbiturate in small dosage—such as 34 gr. amobarbital two or three times daily—to counter the more persistent effects. As with ephedrine, drug tolerance slowly develops, and it is advisable to change from racemic epinephrine to norepinephrine and then perhaps to switch back at a later date, after the tolerance appears to have diminished again to the original substance.

The use of nebulized epinephrine and norepinephrine is not confined to the use with the hand nebulizer. Power-driven nebulizers in the acutely ill patient are convenient to use. Perhaps the most useful application is in combination with intermittent positive pressure breathing devices, which have the merit of improving the bronchial toilet, re-inflating atelectatic lobules, and distributing the medication more evenly throughout the bronchial tree. In either the dyspneic patient with chronic wheezing or the patient with an acute exacerbation, the combination of nebulized epinephrine with intermittent positive pressure breathing (IPPB) is of great service. However, the indications for IPPB must be understood, since there are a few patients, particularly those with bullous emphysema, who may be made worse. A careful trial of this method of administration usually serves to see whether it will be useful.

With the use of IPPB with epinephrine, the majority of acute cases of exacerbation of wheezing come under control. A number of chronic patients may receive enough benefit to be able to increase their activity and to diminish their discomfort. In some cases it is necessary to use other medication, together with the epinephrine group of bronchodilators. Yet it might be said that these substances in nebulized form, when applied with IPPB, are now the mainstay of our treatment of bronchospasm, bronchial mucosal edema and mucus plugging.

Amphetamine and certain related compounds present a strong vasoconstrictor effect. Many of these agents produce a prolonged blanching of the mucosa but a more marked rebound hyperemia than is desirable. Thus, despite the desirability of a more prolonged effect, the picture over all is one of limited usefulness. It must be emphasized that, although the effect of nebulized epinephrine or norepinephrine is relatively transient, therapy can be repeated as needed with still a low toxicity.

#### THE PARASYMPATHETICOLYTICS

These substances act by the inhibition of the effects of acetylcholine in the body, and a very large number of physiologic mechanisms may be affected by their administration. They inhibit bronchial muscle contraction and reduce the production of profuse mucus. They also inhibit salivary glands, gastrointestinal motility, and so forth. Thus, in full dosage these substances may have somewhat unpleasant side-effects. Some derivatives appear to show more specificity for particular sites of action than do others. We have been interested in our laboratory in the study of methyl scopolamine nitrate (Pamine). This appears to have relatively little effect on secretion of the salivary glands until a considerable dosage is reached. Its more distant effects do not seem to be troublesome. At the same time, some pharmacologic effect on the bronchial tree in oral administration of this substance can be demonstrated. As with all of these agents, individual tolerance usually requires modification of dosage from time to time. Toxicity is relatively easily noticed by the appearance of dryness of the mouth. This drug is a useful adjunct when administered in the manner in which one uses ephedrine.

The application of parasympatheticolytics to aerosol therapy has proved to be somewhat disappointing for routine use. Most of these agents have an effect on the mucous membranes, and drying of the mouth in the use of the nebulized agents proves to be a disadvantage. However, in the patient who is not responding to nebulized epinephrine in the acute episode, one will occasionally see benefit. This suggests that there is a secondary factor in epinephrine fastness beyond the factor of route of administration. We would reserve nebulized preparation of parasympatheticolytics for the acute case who is not responding to other forms of treatment.

Abbott <sup>8</sup> has investigated Banthine which, in large dosage, appears to have an advantageous effect upon bronchi. Here the dose appears to be large, and problems of gastrointestinal side-effects are to be considered; however, further work along this line is necessary. It is clear that we are returning to the use of parasympatheticolytics, having moved almost completely away from them toward the sympatheticomimetics. They appear to be less potent than sympatheticomimetic agents, but yet have a role in the treatment of this type of disease.

#### THEOPHYLLINE-ETHYLENEDIAMINE AND OTHER COMPOUNDS

Aminophylline, like the parasympatheticolytic drugs, had passed into relative disuse but is now coming back into popularity. It requires systemic administration and in the United States is not used in nebulized form. The effect is generalized in doses of 0.5 gm. intravenously, administered slowly. The patient with obstruction to expiration is affected at three main points. There is relaxation of the bronchial musculature, the cardiac output is in-

creased, and, lastly, increased respiration results from central stimulation. Under the circumstances, the effects of administration of an adequate dose of aminophylline may be quite dramatic in a patient in whom spasm of the bronchi plays a major part, together with some retention of secretions. It is not only that the bronchi become wider, but also that, with the more effective respiration, secretions may be coughed out and their obstructing effect thereby diminished. The preferential routes of administration are first, intravenous, and second, by rectum. The use of suppositories containing 0.5 gm. of aminophylline is fairly widespread. This has some use in exacerbation of bronchospasm and hypersecretion over the short term; however, such suppositories in the long run are irritating and may produce a granular proctitis. This type of medication is more particularly useful in the young asthmatic than in the chronic bronchitic, and is of little or no use in the patient with senile emphysema. Its usefulness is much enhanced by the co-administration of nebulized bronchodilators and other therapeutic approaches to the problem.

The oral administration is more controversial. There is a definite gastrointestinal irritation in the use of uncoated tablets of aminophylline, and the effect, in our experience, does not appear to be profound. The use of prolonged release preparations may offer a little more—yet it does seem that, used orally, it is not so powerful a substance as some of the nebulized bronchodilators that are in common use, and its application at present there-

fore appears to be limited.

The nitrites, although used considerably in antiquity for the relief of wheezing, are now by and large considered to be obsolete, since the effects are indiscriminate if sufficiently powerful agents are used. The resulting vasodilatation of the mucosa may defeat any alteration of bronchial tonus.

#### MECHANICAL APPROACHES TO THE PROBLEM

The simplest mechanical approach to bronchodilatation is the interposition of a resistance to expiratory flow building up an increased bronchial intraluminar pressure and diminishing the collapsing pressure gradient. Many patients have empirically discovered this themselves and use "pursed-lip expiration" to control dyspnea. This may be of considerable benefit and should be explained in detail to the patient. Where dyspnea is extreme the patient is usually unable to manage this maneuver; in the absence of other equipment, an expiratory resistance mask may be of help. The sole disadvantage is that a resistance to expiration increases the work of breathing and thus increases fatigue, a very significant factor in acute exacerbations of wheezing. Essentially, the resistance to expiration acts by preventing bronchial collapse as the effort to breathe out increases. A similar effect is seen in the patient who has been trained in quiet, non-effortful expiration. In this case, instead of increasing the intraluminal pressure to reduce the gradient, the extraluminal pressure is not allowed to rise. We find that this

is difficult for most dyspneic wheezing patients but that, in combination with pursed-lip expiration, it materially improves their comfort.

This brings up the question of exercises in wheezing patients, considered from the point of view of preventing expiratory bronchial collapse. Diaphragmatic coordination and strengthening will undoubtedly assist in producing both maximal inflation and control of the expiratory phase, as well as development of the abdominal musculature and mobilization of the rib cage. Although objective changes in physiologic measurements may not be obtained, the patient will complain less of discomfort both at rest and on exercise in many cases. In asthmatic children, these exercises are of great importance in the prevention and treatment of chest deformity, with resulting respiratory inefficiency. In adults the effects are less dramatic but still worth while.

The use of binders, belts or pneumoperitoneum to elevate the diaphragm in patients with reduced lung tension has been disappointing in our hands. Actual reduction of the thoracic volume by these means produces an exacerbation of the bronchial collapse. However, where these technics are used to stabilize the diaphragm there may be some benefit. The criterion for such therapy suggested by Barach <sup>9</sup> is improvement of ventilation in Trendelenburg's position, seen in many patients with emphysema. We feel that such improvement of ventilation is due to a redistribution of ventilating alveoli produced by a change in the axis of the hydrostatic pressure in the thoracic cavity. Thus, where the emphysema is chiefly in the upper lobes, improvement may be seen. Our use of such therapeutic methods is therefore confined to stabilization and retraining of diaphragmatic function.

The effects of intermittent positive pressure breathing alone on obstructed expiration are most beneficial in patients in whom obstruction by secretions is a major factor. The question often brought up is whether the bronchi are actively dilated by the intermittent positive pressure at the peak of inflation and, if so, whether there is sustained benefit from this. At present this question cannot be answered, but it seems that benefit may exist. Fowler 10 has noted that the effect of intermittent positive pressure alone is usually far less than when it is supplemented by the use of bronchodilators. Yet this does not rule out a possible beneficial factor. The use of intermittent positive pressure breathing with bronchodilators is well established and has already been referred to. The factor of improved bronchial cleansing. together with widest distribution of medication, makes intermittent positive pressure breathing the most effective method of nebulization therapy. When one is considering bronchial drainage, the use of cough machines and other methods of evacuating viscid secretions must also be considered, particularly in those cases where mucus production and ineffectual cough are the predominant factors. Lastly, the surgical approach to space-occupying lesions may produce bronchodilatation by altering the pressure gradients across the bronchial wall.

#### THE INDIRECT BRONCHODILATORS

Therapeutic measures which reduce mucosal edema or obviate retention of secretions may be considered indirect bronchodilators. Adequate hydration and the use of sputum liquescents, wetting agents and nebulized water diminish the viscidity of secretions. Adequate control of infection with antibiotics and chemotherapeutic agents must be stressed. Desensitization is of value in younger patients in particular. In other patients, corticoids or adrenocorticotropic hormone have proved of great value either in controlling acute exacerbations or on a long-term administration.

Problems of respiratory acidosis, hypoxia and cor pulmonale are beyond the scope of this paper except that therapy aimed at the improvement of ventilation cannot but improve them.

The application and rational route of administration and dosage of direct bronchodilators afford in many cases more immediate relief than does anything else, and act as an integral part of the treatment of the patient.

#### SUMMARY

The mechanisms for the obstructive wheezing found in asthma, chronic bronchitis, senile emphysema and bullous emphysema are discussed. Bronchospasm is a variable part of the mechanism of obstruction but is almost never the whole cause. In the majority of cases it is not an important cause. Therefore, the use of nebulized sympatheticomimetic agents to reduce bronchial mucosal edema as well as relax bronchial muscle, together with basal bronchial muscle relaxation by such substances as ephedrine, appears to offer the most help. Parasympatheticomimetic agents are discussed and their occasional usefulness by nebulization is pointed out; however, it is felt that they belong to the group of drugs best administered systemically. The usefulness and the limitations of aminophylline and other similar agents are considered both in increasing respiration and improving cough, and in providing relaxation of the bronchial musculature. It is realized that the best results with aminophylline will be obtained in the patient in whom bronchospasm and secretions are the major problem.

The direct bronchodilators form only a part of the whole treatment of the patient with obstructive emphysema causing wheezing. Some of the other facets of treatment are briefly outlined. Yet these substances probably form the backbone of treatment of the average case and the best mechanism of using them will provide a better therapeutic result with less systemic toxicity.

#### SUMMARIO IN INTERLINGUA

Es discutite le mechanismo del stertor obstructive que se incontra in asthma, bronchitis chronic, emphysema de senilitate, e emphysema bullose. Bronchospasmo es un parte variabile del mechanismo obstructional, sed illo es quasi numquam le causa complete. In le majoritate del casos illo non es un causa importante. Factores

que es plus importante es edema broncho-mucose, inspissation del muco, e alterationes del resilientia pulmonar. Per consequente, le plus grande ajuta pare esser promittite per le uso de nebulisate agentes sympathicomimetic que reduce le edema broncho-mucose e que relaxa le musculo bronchial, insimul con le relaxation del musculo bronchial basal per substantias del typo de ephedrina. Agentes parasympathetico-mimetic es discutite. Lor utilitate, in certe casos, in forma nebulisate es signalate, Tamen, es opinate que illos pertine al gruppo de drogas que es melio administrate systemicamente. Le utilitate e le limitationes de aminophyllina e simile agentes es considerate ab le puncto de vista del desiderato de augmentar le respiration e de alleviar le tusse e etiam de provider un relaxation del musculatura bronchial. Es admittite que le melior resultatos de aminophyllina se obtene in patientes in qui bronchospasmo e secretiones es le problema principal.

Le bronchodilatatores directe forma solmente un parte del tractamento complete del patiente con obstructive emphysema como causa de stertor. Altere aspectos del tractamento es delineate brevemente. Sed iste substantias forma probabilemente le elemento cardinal del tractamento in le caso typic, e le melior mechanismo in lor

uso provide un melior resultato therapeutic con minus toxicate systemic.

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# MEDICAL EDUCATION

# DEPARTMENTS OF MEDICINE IN 1970. I. STAFF POLICIES\*

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OPTIMAL progress in medicine necessitates systematic planning for the distant as well as the immediate future. Many changes from some of our present patterns are indicated by (a) the tremendously rapid accumulation of medical knowledge, (b) the great improvement in medical facilities, (c) the rapidly increasing availability of good care for all subjects, made possible through improved communication, transportation and economic support, and (d) the public's as well as the scientists' keen interest in excellent medical care, research and teaching.

In seeking information that might be helpful in formulating many future policies for departments of medicine, I recently composed a questionnaire and submitted it to the chairman of each department of medicine in the United States. A total of 82 † received these questionnaires, and thus far 65 have replied; several of the remaining group have signified that they plan to submit their replies later.

Subsequently, virtually the same questionnaire was submitted to another group of physicians who were full-time staff members in departments of medicine. Seeking answers more consistent, in certain respects, than those obtained from the first group, I sent the questionnaire only to those who were between the ages of 38 and 50 and who are or were members of the American Society for Clinical Investigation or the Association of American Physicians. There were 134 in this group; replies have been obtained from 76, and they continue to be received.

The status of medical schools today varies enormously with respect to physical features, objectives, financial support, size of classes, type and number of staff, and in many other ways. Thus, in order to create more of a common denominator for considering plans, the questions were composed with certain premises laid down which the questionees were urged to bear in mind, whether or not they approved of them:

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† Since the clinical situation at Harvard Medical School is divided, the head of the

medical service at each of the four main hospitals was sent a questionnaire.

1. The plans are for approximately 1970.

2. Each questionee was asked to sever himself from his present medical school and hospital, and to project himself into the position of designing a department of medicine in a new school.

3. Only one hospital is utilized by each medical school, and it is under control

of the school.

4. All patients are pay-patients, because of their own savings, insurance plans, or government support. (The city hospitals and veterans hospitals would not continue to operate in the present manner because their patients can be visualized as having become private.)

5. All patients are referred by physicians.

6. All patients are used in the teaching program.

7. You are privileged to reject the patients who are not most useful in teaching and research.

8. An optimal number of full-time staff members is available.

9. A strict, full-time financial system is in effect \* (i.e., the financial remuneration is essentially a salary; it has no particular reference to the number of patients seen).

Since the questions were composed with these premises in mind, and the respondents were encouraged to answer them accordingly, a brief discussion of the premises is indicated. In the development of medical schools, many patterns have evolved that are not ideal. Although economic restraints, lay and/or medical politics, jealousies and other emotional factors have played a significant role in guiding the formation of medical schools, a frequent and significant factor is the failure to formulate a master plan which takes into account future needs as well as the expedient ones. Even though some of the systems are recognized as inadequate and/or inefficient, inertia precludes changing them. Such changes often involve a momentary increase in expenditure of effort and money, but the heightened efficiency resulting may conserve both. In many instances, inefficient systems not only continue to prevail in older schools, but also are instituted in a completely new school, where the problems of changing personnel, buildings, curricula, etc., do not exist. In both old and new schools it is important to formulate what seem to be ideal plans for a distant future, even though complete agreement as to what is "ideal" will not be obtained, and even though many features of the plans will not be evolved in the manner desired.

To get the respondent to think more in ideal terms, he was asked to visualize himself as leaving his present situation and being involved in setting up a new school under "reasonably ideal" conditions. To me, the premises listed seem

<sup>\*</sup>In the formulation of a strict, full-time system, it is important to avoid plans consisting of the corporate practice of medicine, the criticism of public subsidization for the personal benefit of a select group, exploitation of the clinicians by the university, excessive admission of patients, or excessive service in patient care alone by individual staff members.\(^1\) The primary purposes of a university hospital are for teaching and research, so all plans should put major emphasis on these. The support of the practicing physicians is greatly needed, and their views should be given thorough consideration; there should not be unfair competition. The premises given in this paper bear these points in mind. A system that avoids designation as corporate practice is one recently adopted in this school, and is as follows:

(1.) Fees for professional services will be set by and charged in the name of the responsible physician or physicians. (2.) Fees collected for professional services will be deposited in the account of the responsible physician or physicians. To avoid the criticism of subsidization, the following measure has been adopted: A charge will be made by the medical school against these collected fees to cover direct and indirect costs for facilities and personnel.

realistically ideal, except the one requiring that all patients be referred by physicians. This one, of course, has the disadvantage of denying as much freedom as the full-time staff desires. However, the physicians in practice deserve protection from unfair competition. Furthermore, the more considerate practicing physician can help in selecting patients who are most needed for teaching and research.

In the selection of the year 1970 as one toward which we should plan, there was an attempt to apply realism in idealism. This would allow time to make psychologic, financial and other adjustments, but seemingly the interval is not long enough for so many changes to occur as to make extrapolation too erroneous.

Actually, we should start instituting many of the plans now.

Some of the other premises will be discussed in conjunction with the analysis of the replies to the questions, which will be presented here. The questions are repeated here exactly as they were submitted to the questionees. Some of the questions were readily answered, whereas others necessitated considerable thought. In some instances the questions were not answered, either because they were not considered to be clear, or because they seemed too difficult to evaluate; in most instances these will be mentioned as the respective questions are discussed. The respondents were encouraged to make comments regarding the questions as desired; these have been carefully studied, but are not quoted here because I have no way of knowing how often the reactions expressed were shared by the other respondents, except by the categoric answers. In order to tabulate the replies, most of the questions were composed to call for a categoric answer. However, it must be emphasized that the answer to some questions depends upon the weight given to many influencing factors, which may differ among various staff members, making it necessary to obtain the opinion of many. Therefore, the exact numbers listed in the replies to these contingency questions should not be considered rigidly.

#### FULL-TIME STAFF

# NUMBER AND ROLE OF SPECIALISTS\* AND DIVISIONS IN MEDICINE

Number and Field of Staff Members Desired

Indicate how many of the following Specialists are desired for optimal teaching and research in a Department of Medicine. If none of a given type is desired, write zero.

Allergists	Oncologists	Microbiologists
Dermatologists	Geneticists	Gerontologists
Neurologists	Generalists †	Hematologists
Endocrinologists	Renologists	Rheumatologists
Cardiologists	Gastroenterologists	Pharmacologists
	Nutritionists	Isotopists
Others (specify)		

\* The term "Specialist," as used in this questionnaire, is applied to one who specializes in one phase of internal medicine.

<sup>†</sup> Physicians designated here as "Generalists" are regarded as broad-spectrum internists, not confining their practice to any particular specialty in medicine. As specialization increases, and as the scope of each field is narrowed, the "Generalists" can serve an increasingly important role in coördination. (Because this term is also used sometimes for General Practitioners, I have decided to use instead, in this paper, the designation "General Internists.")

In the course of our asking how many different full-time specialists, including general internists, were desired, information was obtained relative to the total number of staff needed; this information is revealed in figures 1 and 2. The Chairmen (Chm.) desired an average of 32, with a range of from 11 to 64. The number employed at present averages 15, including five paid largely from research or teaching grants. It is of note, however, that three desired fewer than

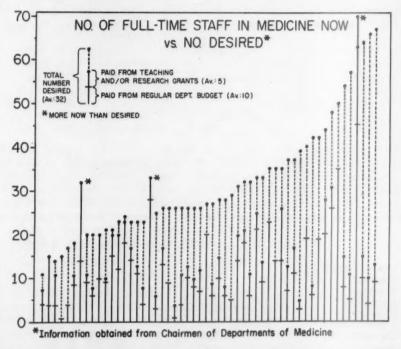


Fig. 1. Neither this figure nor any of the others contains data from a few respondents whose data were late in arriving.

at present, but each of these three has more than 30 (one 70) at present. The number desired by Nonchairmen (Non-Chm.) was 26, with a range of from eight to 70.

As shown in figure 3, there was marked variation in the number of full-time specialists desired for the department of medicine in each medical school. As anticipated, there were votes for more general internists than for any specialist group. Seven of the Chm. and five of the Non-Chm. indicated that there should be 10 or more general internists, but more than one-half of the Chm. and Non-Chm. suggested that there be four or less. The number of general internists needed depends, of course, upon the extent of training, experience, and indul-

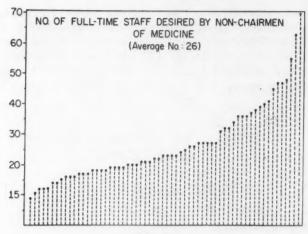


Fig. 2.

gence in general internal medicine by the specialists. The general internist plays an important role, in dealing with diffuse problems as well as with the many single problems that he is prepared to handle. Also, he coördinates many activities of the specialists. However, as discussed later, the specialist should receive a broad training in general internal medicine, and should have a good perspective on problems outside of his field. Whereas it is nice in principle to

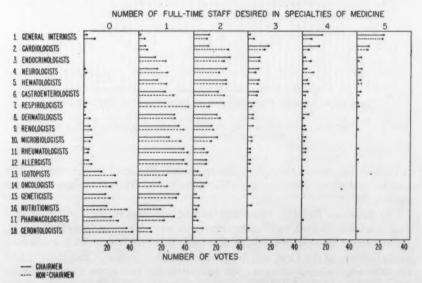


Fig. 3. The specialists are ranked in order of the total number desired. As expected, there was considerable variation in the number selected by the respondents.

have chiefly staff members who have acquired most of the available knowledge in all of the specialties, this usually is too great an undertaking. Such a goal is even more remote for one who wants to be an expert in a specialty. As discussed recently, many specialists are needed, working together as a team, with nice coördination of the activities of the various staff members.

My impression, based on figure 3, as well as on other observations, is that there is not full appreciation of the need for isotopists, oncologists, geneticists, pharmacologists and gerontologists. The gerontologist should be the counterpart of the pediatrician, each specializing in the problems offered by the extremes of age per se; but many of the difficult systemic problems should be handled by

a specialist in the respective field.

Other full-time specialists considered by a few respondents as desirable in a department of medicine are: biochemist, physicist, psychosomaticist, electron microscopist, administrative officer, peripheral circulationist, physiologist and cellular metabolist. None of these was listed more than four times either by Chm. or Non-Chm., except for biochemist, which was indicated seven times by Chm. In our Department of Medicine we have eight full-time biochemists, and find them of distinct value in both teaching and research; our need for a physicist is great.

Organization and Responsibilities of Divisions: Now that there is evidence that most of the respondents believe that many specialists are necessary, certain problems relative to administrative policies pertaining to them are to be con-

sidered. The following question was asked:

Should any of the specialties (previously listed) be set up as a department, independent of the Department of Medicine?

	Yes	No
Chm.	11	49
Non-Chm.	14	54

It is clear that only a relatively small number of respondents favored a departmental status for any of the specialists discussed. My reaction is that either none of them should have this status (except under unusual circumstances), or most of them should have it, because their problems are similar. We have found the situation appropriately handled at present by developing strong divisions, with good coördination of activities between divisions. However, with a marked increase in "vertical" teaching and research, considerable independence is indicated.

The advantages and disadvantages of giving some of the specialties of medicine the status of a department should now be considered. Representatives of some of these fields lead vigorous fights for departmental status, because they believe that when their specialty is in a department of medicine they may be given (a) too little independence in dealing with the teaching, research, patient care, and administration pertaining to their respective interests, (b) too little office and laboratory space, staff, budget and curriculum time, and (c) too little respect. Such criticisms have often had a good basis, but the opposite extreme to which many have gone has often led to a net worsening of the situation. The independence has occasionally become so extreme that there has been marked fragmentation in the teaching of students, and house officers in medicine may

receive no training in a certain specialty. -Moreover, the isolation of the specialty often decreases the number of students and house officers who make it their career.

Neither of the foregoing extreme situations is desirable, and both should be corrected. This can be done by establishing strong divisions with considerable independence, all operating under common policies formulated after due consideration of the opinions from representatives from each of the specialties. There should be excellent coördination of the specialties and fairly equitable consideration of the needs of each. There will not be over-all optimal progress unless there are good teamwork and spirit.

The answers to the following questions illustrate the opinions of others relative to establishing divisions and certain administrative policies pertaining to them:

Should each specialty represented by a full-time staff member be considered essentially to be a Division of Medicine?

	Yes	No
Chm.	34	25
Non-Chm.	46	25

Should each Division be given considerable independence relative to teaching, research, administration and patient-care, as long as it conforms to the policies of the Department, and as long as it participates in the teamwork indicated, and integrates its patterns smoothly with the master plans for the Department?

	Yes	No
Chm.	49	9
Non-Chm.	59	12

If there is more than one staff member in a particular specialty in a Department, should a specific physician be designated as Director, Head or Chief of the Division, and be responsible for the administration of the Division?

	Yes	No
Chm.	53	6
Non-Chm.	60	10

Should it be the objective of the Chairman of the Department to deal more or less equally with the Divisions with regard to allocations of departmental funds, office space, laboratory space, number of hospital beds, etc.?

	Yes	No
Chm.	16	43
Non-Chm.	27	45

My own answers to the first three of the foregoing questions are in the affirmative, but, as indicated by other respondents, certain circumstances could modify the decisions. With regard to the last question, I wish to state that, at present, all of the full-time staff in our Department of Medicine are in one or another Division, and each Division is given essentially the same advantages. There are of course some differences, e.g., space—some specialists readily agree that they need less space than do others. Moreover, the person who does not take appropriate advantage of the opportunities presented deserves less permission to expand than one who does. The allocations of budget, space, etc., should not be based on the number of patients with a particular type of disorder, but

Table 1
Number of Beds That Should Be Available to Medicine

No. Beds	100	150	200	250	300	300+
			Number	of Votes		
Chm. Non-Chm.	9	7	18 15	4 6	8 7	8 3

upon the over-all needs for optimal teaching and research. Some specialties hold far more prestige nationally and are given more attention in many ways than are others. Consequently, the latter may have such poor facilities for teaching and research that few (and inferior) men are attracted to them; in this manner a vicious cycle is set up. Highly capable staff men can lend great prestige to any division, but it is of course easier if they are given appropriate support. Such specialties need extra attention because there is much that they can offer if properly nurtured.

The development of strong Divisions which are granted considerable freedom often helps in the coördination of activities of the respective specialists in other departments. With the growing tendency for an increase in vertical teaching (which I favor to a marked degree), the aforementioned coördination and collaboration are much needed. Moreover, it seems reasonable for a specialist in medicine to provide consultation and/or care for patients on other services with major or perplexing nonsurgical problems in his respective field, unless there is very good indication for the nonmedical department to have such a staff representative of its own.

Responsibilities in Patient Care: In a department of medicine, so much of the teaching, research and administration involves patients that it is highly important that the policies established relative to patient care be designed to meet most effectively and efficiently the needs for teaching and research. As mentioned earlier, it is desirable to accept only the type and number of patients that supply the teaching and research needs, and what professional fees are collected should be coincidental to these academic functions. With these major considerations in mind, the following questions were asked:

How many beds should be available to Medicine?

All but two respondents thought the Department of Medicine needed at least 100 beds or more. As shown in table 1, the mode was 200 beds.

The answers to the next two questions demonstrate that very few of the respondents thought that there should be a relatively even distribution of beds among the Divisions in Medicine. Whereas the majority preferred not to group together on the ward patients under the supervision of a given Division (except communicable diseases), there was a significant number that favored such a plan.

Should there be a relatively even distribution of beds between the Divisions in Medicine?

	Yes	No
Chm.	5	52
Non-Chm.	8	58

Should the patients under the supervision of a given Division be grouped together on a ward?

	Yes	No
Chm.	18	36
Non-Chm.	23	39

All patients should have an excellent general examination periodically, and if the specialist to whom the patient is referred is not capable of such, the patient should be examined by one who is. It is my desire that all staff members in the Department of Medicine possess this ability. The General Internist plays an important role in dealing with diffuse problems, and sometimes in coördinating activities when several specialists are involved. The following two questions reveal the opinions of the respondents along these lines:

Should most of the patients be examined by a General Internist or one serving in this capacity, even though they are to be seen by a specialist (not in the Department of Medicine)?

	Yes	No
Chm.	51	7
Non-Chm.	58	13

Is it desirable to have a general internist serve as a coördinator in dealing with many of the patients seeing several specialists?

	Yes	No
Chm.	50	6
Non-Chm.	57	14

Advantages in patient care, teaching and research are served when specialists, additional to those from Medicine, are stationed in the Medical Clinic. This view is amply supported in the responses to the following question:

Do you favor an arrangement in the Outpatient Department whereby a few specialists from Departments additional to those from Medicine are stationed in the Medical Clinic part of the time, or are "on call" whenever their presence is desired?

	Yes	No
Chm.	56	3
Non-Chm.	57	11

# APPOINTMENT, SALARY AND RESPONSIBILITIES OF FULL-TIME STAFF, EXCLUDING CHAIRMAN

Preferable Stage of Development for New Staff Member:

In general, in the acquiring of a new staff member as the first specialist for a given Division in Medicine, who is preferable:

(a) One who has had, in addition to residency training, two years of research fellowship training and then approximately three years in an independent status?

	Yes	No
Chm.	30	5
Non-Chm.	32	13

(b) One who is well established and has already attained approximately an Associate Professor level?

			Yes	No
		Chm.	7	15
		Non-Chm.	17	24
(c)	Intermediate?			
			Yes	No
		Chm.	26	4
		Non-Chm.	19	17

It is apparent that most of the respondents (as do I) prefer selecting a person who is at a fairly early stage in his career. However, it is desirable that he should have demonstrated excellence in the following five categories: (a) teaching, (b) research, (c) administration, (d) patient care, and (e) personality characteristics. At least the background should be sufficient to enable a reasonably good extrapolation of his future. The young individual is more apt to enter into the team spirit and to show enthusiasm. Moreover, the years during which he is "blossoming" are often the most productive in his research career.

#### Staff Salaries:

Assuming that your school will have a "strict" full-time system (i.e., that the financial remuneration is virtually a salary, and that the salary will have no particular reference to the number of patients seen), and assuming that you have an appropriate budget, and that the economic standards in general are maintained at the present level, list the annual salary ranges you consider appropriate for full-time staff members in your Department of Medicine:

	Chm.	Non-Chm.
	(Avera	ge Amounts)
Instructor	\$ 9,111	\$ 9,000
Assistant Professor	\$12,272	\$11,500
Associate Professor	\$16,545	\$15,500
Professor (not Chm.)	\$20,333	\$19,833
Professor and Chm.	\$24,769	\$24,214

Figure 4 shows the salary selected by each respondent for the different staff ranks. Marked improvement in the teaching and research would occur if there was elimination of the time spent in seeing private patients just to increase the staff member's income. In the teaching and research programs it is preferable to utilize the paying patients with the nonpaying (until such time as all are paying patients), giving each the same excellent care.

The time is rapidly approaching when, through one means or another, essentially all of the patients will be paying patients. Since professional fees will be collected, questions arise as to the most efficacious plans for dealing with them.

With the strict full-time scheme previously indicated, it is probable that the total amount of money collected for professional fees will exceed that needed for appropriate supplementations of the salaries of the clinical staff.

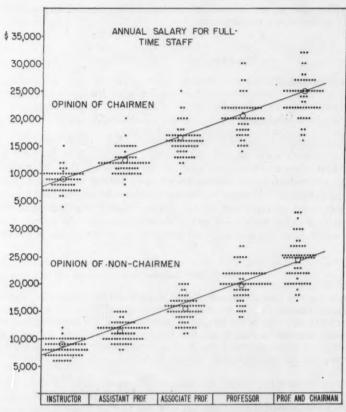


Fig. 4. The large circles indicate the average of the salaries selected. The linear progression and the closeness of the figures selected by the Chairmen and Nonchairmen are notable.

- (a) Please indicate the approximate percentage of the excess that should be spent in the following categories. If you are opposed to allocating it to a specific category, indicate with a zero.
  - (1) Additional clinical staff .....
  - (2) Additional basic scientists in clinical departments . . . .
  - (3) Research fund for clinical departments .....
  - (4) Supplementation of salaries in basic science departments .....
  - (5) Research fund for basic science departments .....
  - (6) Other .....

As can be seen in table 2, the majority of the respondents favored using the excess funds for one or more of the six categories, but there was considerable variation of opinion as to the percentages that should be allocated to each. More favored allocation to a research fund for the clinical departments than for the other categories. A great majority favored pooling enough money for supple-

TABLE 2
Allocation of Funds from Professional Fees

Per Cent of Funds		0	1-10	11-20	21-30	31-40	41-50	50-4			
			For add	itional cli	nical staf	f					
	Chm. Non-Chm.	16 19	5 3	12 8	12	3 2	5 7	0			
	For additional basic scientists in clinical departments										
	Chm. Non-Chm.	13 16	10 3	15 10	12	0	0 4	10			
Number	For research fund for clinical departments										
of Votes	Chm. Non-Chm.	5 7	8 2	8 10	8 16	7 3	8 14	2 4			
	For supplementation of salaries in basic science departments										
	Chm. Non-Chm.	14 18	6 5	14 11	9	3	5 6	0			
		For resea	rch fund	for basic	science de	epartmen	ts				
	Chm. Non-Chm.	18 21	6 8	7 9	5 3	0	1 1	0			

mentation of the salaries of all the full-time clinical staff, as indicated by the replies to the following question:

Do you favor pooling enough money from all of the clinical departments to assure appropriate supplementations of the salaries of *all* of the full-time clinical staff?

	Yes	No
Chm.	45	12
Non-Chm	56	10

A smaller number favored allocations from such a fund to any of the aforementioned six items, as elicited from the following question (table 3):

How many of the items in the above list should also be taken care of from such a general pool?

In answering the next question, a slight majority indicated that each clinical department should be permitted to keep a portion of the earnings by its staff via professional fees.

Should each clinical department be granted permission to keep a given percentage of its earnings via professional fees, irrespective of the needs in the categories listed above?

	Yes	No
Chm.	31	25
Non-Chm.	38	30

TABLE 3

Votes Favoring Allocations from a Pool of Professional Fees (Derived from All Clinical Departments)

	Chm.	Non-Chm.
1. For additional clinical staff	27	29
2. For additional basic scientists in clinical departments	33	34
3. For research fund for clinical departments	35	37
4. For supplementation of salaries in basic science departments	29	27
5. For research fund for basic science departments	21	15
6. Other	. 10	8

Amount and Priority of Time Spent in Teaching, Research and Administration: Since there often is discussion as to the amount of time that should be spent respectively in teaching, research and administration, and the priorities that should be assigned in case of conflict, the following questions were asked:

Although it is thoroughly realized that teaching, research and administration usually go hand-in-hand, there is often a primary emphasis on one or the other. With this in mind, please indicate the proportion of time that should be spent in each. (Committee meetings, public relations, etc., should be included with administration. Assume that you will have a strict full-time system, and that essentially all of the patients are paying patients and are used in teaching.)

Admitting that there will be many exceptions, rate in 1-2-3 order the priorities that your staff should give to their responsibilities in:

TABLE 4

Distribution of Time That Should Be Spent by Nonchairman

Per Cent	1-10	11-20	21-30	31-40	41-50	51+
Teaching	0	1	14	26	15	3
Research	0	3	8	27	16	5
Administration	19	32	5	0	2	0

As is seen in table 4, almost all of the respondents thought that the staff, excluding the chairman, should spend less than 21% of its time in administration, and the remainder approximately equally in teaching and research. The order of priority chosen, as shown in table 5, was clearly as follows: (a) teaching, (b) research, and (c) administration. This order should, of course, be shifted in accordance with the relative importance of the problems competing at a given time. However, individuals assign different degrees of importance to the same set of problems. It is my impression that the importance of prompt and wise handling of administrative problems is greatly underrated; if they are not dealt with appropriately, the teaching and research of many people may be seriously hampered. I am in agreement that most of the Non-Chairmen should spend far less time in administration than in teaching and research, but the responsibilities accepted should be handled well. As is discussed later, there

is common agreement that the chairman is overloaded with administration, and that it is desirable for others in the department to share some of the burden. In recent years there has been a tendency on the part of some staff members to favor research and to neglect their teaching duties, qualitatively as well as quantitatively. The major reason for this negligence is the general failure to attach sufficient significance and glamour to skillful administration and teaching; these factors are given too little consideration with respect to promotion in faculty rank. The situation is likened somewhat to football, and the underrating of the linemen and blockers in comparison with the ball carrier.

Tenure: It is important for each full-time staff member to attain a high academic level and to maintain it. Some of the staff may not reach the high level of development that seemed probable earlier, and some may fade soon after reaching a high level. One of the problems is to deal appropriately and diplomatically with those who have such fates. The following question relates to one of these phases:

Some schools have a policy demanding that tenure be granted within a specified time, or that a staff member not be permitted to continue in a full-time capacity without such tenure. Do you favor this policy?

	Yes	No
Chm.	33	28
Non-Chm.	42	29

The majority favored changing the status of the staff member who does not perform at a sufficiently high level. The establishment of a common policy of this type makes it easier for the chairman of the department to handle such problems. The person with tenure who has performed well and then faded may benefit if some of his problems are corrected, if some of his responsibilities are changed, or if he is granted a leave of absence to spend several months in another medical center.

TABLE 5
Recommended Priorities for Responsibilities of Staff (Excluding Chairman) (Not Total Time)

Priority	One	Two	Three
		Number of Votes	
Teaching	52	5	0
Research	4	43	10
Administration	1	7	48

#### Leave of Absence:

Do you favor the institution of a system that will strongly encourage most staff members to take a periodic leave of absence for study or research in other medical centers?

	Yes	No
Chm.	58	3
Non-Chm.	67	5

Granting that the duration and frequency of such should vary with different individuals, what do you visualize as an average approximate amount?

Frequency	of	leaves	-of-a	bsence	 	0 0	0 0		years
Average di	ıra	tion of	each	leave	 			11	nonths

TABLE 6
Leave of Absence

	Frequency					Duration						
Years	1-2	3-4	5-6	7-8	9+	Months	1-2	3-4	5-6	7-8	9-10	11-12
					Num	ber of Votes						
Chm. Non-Chm.	4 3	14 13	31 32	10 16	1	Chm. Non-Chm.	6 3	9	22 27	0 5	8	13 14

Most of the respondents favored a policy of granting leaves of absence, with the mode of frequency being from five to six years, and the mode of duration being from five to six months (table 6).

## RESPONSIBILITIES, SALARY AND TENURE OF THE CHAIRMAN OF THE DEPARTMENT OF MEDICINE

Amount and Priority of Time in Teaching, Research and Administration Spent by Chairman:

Many factors compete for his time. Indicate in 1-2-3 order the priorities that you consider should generally apply: Administration ....., Teaching ....., Research .....

Indicate roughly the proportion of time that should be spent in the following, bearing in mind the assumptions that were enumerated previously relative to the other full-time staff members: Administration .....% Teaching .....%

Unlike the situation in table 5, dealing with Non-Chairmen, table 7 shows that the majority of the respondents believe that the Chairman should give first priority to administration, second to teaching, and third to research. Table 8 reveals that the majority of the respondents believe that the Chairman should spend most of his time in administration, with teaching next in importance, and research last. These conclusions are in accord with my own emphatic opinions.

TABLE 7
Recommended Priorities for Responsibilities of Chairman

	(Not Total	Time)	
Priority	One	Two Number of Votes	• Three
Teaching Chm. Non-Chm.	21 37	37 31	2 2
Research Chm. Non-Chm.	3 5	. 7 17	50 48
Administration Chm. Non-Chm.	38 33	15 21	7 16

Table 8
Distribution of Time That Should Be Spent by Chairman

Per Cent	1-10	11-20	21-30	31-40	41-50	51+
Teaching	0	5	20	16	. 9	1
Research	3	14	31	9	1	1
Administration	2	5	17	16	17	2

Since the duties of the Chairman differ in many respects, particularly in degree, it is difficult to know at the time of his appointment how well he will perform. Moreover, there are many who do well for only a while. There are also some who, within a few years, are capable of tremendous accomplishments in administration and then are needed for research and teaching. With these factors in mind, the following question was asked:

If no reduction in salary resulted, would you favor limiting the period as Chairman to:

	Chm.	Non-Chm.
10 years	14	5
15 years	11	12
20 years	2	5
No limitation	39	47
(except age 6.	$5\pm)$	

The great majority of respondents concluded that there should be no limitation in the time of service, except for age retirement. However, I am in favor of trying a system of the following type:

Establish 15 years as a standard period. It takes this amount of time to attain the goals for many of the long-range plans. Moreover, it requires several years to become adept in the position. Since, however, some Chairmen do a job inferior to what was anticipated, I believe that, at the end of five years, further tenure as Chairman should be based upon approval of the Dean, the majority (or perhaps a two-thirds vote) of the full-time staff in the Chairman's Department, and the majority of the Chairmen of other Departments. With this approval he would continue for a total of 15 years, and be re-appointed at five-year intervals thereafter, pending approval of the aforementioned groups. Were he not to continue as Chairman, he would hold his professional position and, after serving 15 years as Chairman, would have no reduction in salary, even though he did not continue as Chairman.

Heavy Duties of Chairman and Recommended Changes: With the following questions, opinions were solicited as to whether the Chairman's duties are too heavy and, if so, what readjustments might be made.

Do you believe that the duties of the Chairman have become so heavy that significant readjustments should be made?

	Yes	No
Chm,	49	12
Non-Chm	63	8

Should the Department have what amounts to a business manager or assistant executive officer?

	Yes	No
Chm.	49	12
Non-Chm.	57	16

If "ves." is it preferable that he have:

	M.D. Degree	Ph.D. Degree	Neither
Chm.	26	2	23
Non-Chm.	35	0	23

If "no," should the burden be reduced by dividing the administrative work among other members of the Department?

	Yes	No
Chm.	9	3
Non-Chm.	21	6

It is clearly evident that the great majority of respondents believe that the administrative duties of the Chairman are too great. This was further emphasized in many comments that the respondents made. Considering these, along with my own thoughts, I would make the following suggestions for reducing the Chairman's present duties: (a) reduce the amount he is expected to handle by improving over-all Medical School and University policies, and by having central business offices to relieve him; (b) provide a super-secretarial force; (c) employ a business manager and/or a young physician as an assistant executive officer; (d) delegate more administration to the other members of the Department; (e) set up Divisions and give them considerable responsibility relative to their own problems.

Curtailment in the number and length of forms and length of reports and improvement in general administrative efficiency will reduce the Chairman's load. Much of the work is clerical and does not require a physician to handle it. A large Department should have a layman trained in business administration who, with the help of an excellent secretarial group, should deal with as many of the problems as possible. A relatively young internist who preferably has had his student and house officer training locally can help in many of the professional problems. Some administrative duties can be delegated to various members of the staff. However, the delegation of duties to the many aforementioned groups can lead to more over-all damage than good if not properly handled. It is important for the staff to feel satisfied with the arrangements and to utilize the channels established. If they and the Chairman circumvent these avenues, much confusion and inefficiency will result. In parceling out duties to other staff members it is important to parcel whole packages, and for the Chairman to give support and assistance as needed. The person to whom the job is delegated should usually be given considerable authority in executing it. When a given task is interrelated with many others and has a complex background it can seldom be delegated satisfactorily.

If the Chairman is relieved of some of the minutiæ, he can play a greater role of leadership in medical education and in research. He will also have more time to deal with major policies that are of importance to many staff members, inside

and outside of his own Department. He also will have more time to teach, which will thereby bring him closer to students, interns, residents, research fellows and trainees. In this connection, it is not the facts alone that he presents, but the inspiration and the aid that he gives to the younger group in the formulation of their careers.

#### RESEARCH

The following questions relate to the extent to which the faculty may or may not engage in research:

What percentage of the full-time staff (M.D.) should be permitted to engage in essentially nothing but research?

What percentage of the full-time staff (M.D.) should be permitted to engage in essentially no research?

Table 9

Per Cent of Staff That Should Be Permitted to Engage Only in Research

Per Cent	0	1-10	11-20	21-30	30+
			Number of Votes		
Chm. Non-Chm.	22	16	15	4	0

As can be seen in table 9, there are many who believe that none of the full-time staff should be permitted to engage exclusively in research. Some of the respondents expressed strong feelings on this subject. However, an appreciable number favors permitting up to 30% to be in this category. Most of the respondents thought that there should be either no, or very few, staff members who do no research (table 10).

TABLE 10

Per Cent of Staff That Should Be Permitted to Engage in No Research

Per Cent	0	1-10	11-20	21-30	30+
Number of Votes					
Chm. Non-Chm.	24	16	10	7 7	2

The manner in which research should be financed has become an increasingly important problem; the next question relates to certain aspects of it:

Assuming that the majority of research funds are not derived from the regular medical school budget, what percentage of the total "outside" research

funds should be given as:

- (a) Project grants .....
- (b) (Established) investigator grants .....
- (c) Departmental grants .....
- (d) Medical school grants .....

Although the vote on this question was widely distributed and there was a close average percentage favored from the different sources, the order of increasing desirability is as follows: medical school, investigator (established), departmental, and project (table 11). Each system has certain advantages and disadvantages in comparison with the others.

TABLE 11
Percentage of "Outside" Research Funds That Should Be Given as:

Per Cent	0	1-10	11-20	21-30	31-40	41-50	50+
			Nu	mber of Vo	otes		
Project grants (Established) Investigator	3	5	10	12	5	10	3
grants	0	11	10	15	6	2	1
Departmental grants	1	4	14	18	6	5	1
Departmental grants Medical school grants	2	13	20	7	1	3	2

#### SPECIAL STAFF

Some Departments are appointing an increasing number of biochemists, biophysicists and other basic scientists who have a Ph.D. degree but no M.D. degree. This group has been considered to be valuable in team research, and in assisting with the teaching of the research fellows and others.

With this group, do you favor using the standard set of professional titles with the word "Research" prefacing them (e.g., "Research Assistant Professor"), or some system similar to this?

	Yes	No
Chm.	46	13
Non-Chm.	52	15

Should each individual in this group have a title in the Department of his specialty as well as in the Department of Medicine?

	Yes	No
Chm.	38	19
Non-Chm	55	13

Do you favor giving tenure to some of the members of this group?

	Yes	No
Chm.	48	8
Non-Chm.	64	4

With the progress of time, some of these basic scientists may become so involved in some of their own fundamental investigations that they no longer participate significantly as collaborators with the clinical staff members. In this instance, do you favor encouraging the basic scientists to shift to a basic science department?

	Yes	No
Chm.	48	7
Non-Chm.	49	19

My own opinion agrees with comments made voluntarily by several respondents, namely, that this group of basic scientists plays a very important role in teaching, research and administration in Departments of Medicine. Many research projects, though strongly embracing clinical problems, soon lead us into fields of basic science, beyond our sphere of training. Therefore, to pursue the projects properly, we need assistance from appropriate basic scientists. Sometimes it is sufficient merely to consult a member of the corresponding basic science department. However, some of the problems are of such magnitude as to make this too much of an imposition. For these reasons it is desirable to have the appropriate basic scientists in the Department of Medicine. This may involve biochemists, physicists or others, but biochemists have been in the greatest demand. To acquire and to keep high quality scientists of this type, it is necessary to provide them with fitting titles, salaries and working conditions. It is hoped that they will want to be genuine collaborators in many research problems. However, it is anticipated that they will desire to work on some research projects that are entirely their own. This should be granted, because they still can serve a very important function in a consultant capacity and in supervising some of the research fellows and technicians. It is important that members of this group advance appropriately in academic circles. They should have such standing that they are sought after by basic science departments and other clinical departments. I have found that such can be the case, based on my knowledge that such men have been offered the Chairmanship of some of the leading Departments of Biochemistry. In dealing with the appointment of this group, the Department of Medicine should work in close relation with the appropriate basic science department. Usually, but not always, it is desirable for the basic scientist to hold a dual appointment, and to participate in some of the activities of each department, but usually with most of his activities in one department or another.

As indicated earlier, we have several biochemists in our department, and have had a mutually satisfactory arrangement not only in research but also in teaching. These men play an enormously important role in teaching the research fellows and trainees in general, and also in specific phases of research. They are helpful too with students, and have done a great deal toward bringing the basic and the clinical sciences closer together. They assist in administrative problems dealing with technicians, laboratory equipment and supplies, and in other ways.

Whether a specific basic science staff member should be encouraged to change to a basic science department will depend upon the individual circumstances. When such is the case, there usually will be a mutual opinion.

#### VOLUNTARY STAFF

The Voluntary Staff, as considered here, is composed of those who give time to the activities of the Department while receiving little or no pay. The following three questions were asked with respect to this group:

Roughly what proportion of the total amount of teaching in the Department should be done by this group:

	60%	40%	20%
Chm.	2	19	25
Non-Chm.	7	26	21

Should thorough, systematic evaluations of each member of this group be sought periodically from the students and the interns and residents, or from both, or from neither?

	Stud.	Int. & Res.	Both	Neither
Chm.	0	5	36	16
Non-Chm.	0	8	43	18

As it becomes evident with the passage of time that such staff members do not have a sufficiently good performance in teaching, through lack of ability, time or interest, which of the following moves relative to their staff appointment would you favor:

	Chm.	Non-Chm.
Complete removal from the staff	33	29
Some type of courtesy appointment	26	42
No change	2	2

Some of the respondents indicated that the voluntary staff should contribute the following percentage of the total teaching (these percentages were not listed in the question): 50% (three votes), 30% (six votes), 25% (one vote), 10% (two votes), 0% (four votes).

The majority indicated that the voluntary staff should do about 20 to 40% of the total teaching, and that these staff members should be evaluated periodically by students, interns and residents. A large number of the respondents stipulated, however, that if such evaluations are obtained, the members of the full-time staff should be evaluated in the same manner. Throughout the 10-year history of our Department, we have had frequent evaluations not only of the voluntary staff but also of the full-time staff; of course, we also obtain evaluations from the other staff members. All evaluations are obtained in a quiet and diplomatic manner. We have found all of these evaluations helpful in improving the teaching of individual staff members, as a guide in making assignments for our staff, and in evaluating our teaching program. When the teaching performance of a staff member is consistently poor, he should either be removed from the staff or given a courtesy appointment, depending upon the individual circumstances. Some of the better members of the voluntary staff are of enormous assistance.

#### CLINICAL LABORATORIES

The clinical laboratories have grown to occupy a major phase in the activities in internal medicine. The number of tests and the proper interpretation of them

are overwhelming problems in the majority of institutions. No one person can master these individual problems. It therefore seems essential that an expert be selected as head for each one of the three major laboratories, the chief duty of each person being to direct the activity of his laboratory. These are highly important positions, and the ones who fill them should be leaders in their fields, making good contributions to them. It is also important to select individuals with a good academic background, and to afford them the opportunity for continued academic development. They should play a significant role in both teaching and research. The replies to the following questions strongly emphasize some of these concepts:

Do you favor appointing three persons, with a Ph.D. and/or an M.D. degree, whose major activities are in one or another of the following laboratories:

	Yes	No
Chemistry (including urin	ne) 57	3
Microbiology	55	5
Hematology	54	6

Should the individuals receiving these appointments be required to have the same high-level academic qualifications as do other staff members in the medical school?

Should they be expected to participate in approximately the same amount of teaching and research as do other staff members?

Should their faculty titles be like others (in the basic science or clinical departments) in their respective specialties?

Yes	No
56	1

#### SUMMARY AND CONCLUSIONS

A questionnaire dealing with some future policies for departments of medicine in administration, teaching, research and patient care was submitted to the Head of the Department of Medicine in each medical school in the United States. A similar one was sent to each full-time staff member in a Department of Medicine who was between the ages of 38 and 50 and who was a member of the American Society for Clinical Investigation and/or the Association of American Physicians. The questions were answered in the light of certain premises embodying some reasonably ideal facilities. Although there were, naturally, differences of opinion, and although some of the questions were difficult to answer categorically, some of the more pertinent points favored by the majority of respondents are presented below.

An average of 32 full-time staff members per Department of Medicine was considered desirable by the chairmen and 25 by the non-chairmen; the average at present is 15. The average number of specialists desired was in the following decreasing order: general internists, cardiologists, endocrinologists, neurologists,

hematologists, gastroenterologists, respirologists, dermatologists, renologists, microbiologists, rheumatologists, allergists, isotopists, oncologists, geneticists, nutritionists, pharmacologists, and gerontologists. Very few respondents favored a departmental status for any of the corresponding specialties. The majority considered that each specialty represented by a full-time staff member should be considered to be a Division of Medicine and, as such, should be given considerable independence relative to teaching, research, administration and patient-care, as long as it conformed to the policies of the Department, and as long as it participated in the teamwork indicated, and integrated its pattern smoothly with the master plans for the Department. Moreover, if there is more than one staff member in a particular specialty, one physician should be designated as Director, Head or Chief of the Division. Each Division should attempt to coordinate its activities with other Divisions and Departments.

In general, when a new staff member is added as the first specialist for a given Division, it is preferable to secure a physician within a few years following completion of his research fellowship, rather than one at the Associate Professor

level, but there are distinct exceptions to this policy.

The average salary should be approximately as follows: Instructor, \$9,000; Assistant Professor, \$12,000; Associate Professor, \$16,000; Professor, \$20,000; Professor and Chairman, \$25,000.

Leaves of absence were favored, on an average of every five to six years,

for intervals averaging from five to six months.

When there is competition for time, the following priority should apply for Chairmen: administration, teaching and research; moreover, the amount of time devoted should be in the same order. With Non-Chairmen, the priority should be: teaching, research and administration; about 10 to 15% of their time was recommended for administration, the remainder divided more or less equally between teaching and research. The Chairman is overburdened with administrative work. Suggestions for improving the situation consisted of one or more of the following: assistance from central offices, improvement in general administrative policies, employment of an assistant executive officer (physician) and/or a business manager, a super-secretary arrangement, assistance from Division heads and allocation to them of considerable responsibility for their own units.

Having more than a few staff members engaging exclusively in research or

exclusively in teaching did not meet with approval.

The number of beds considered by most respondents as desirable for a Department of Medicine was approximately 150 to 200. It was considered preferable not to group together on a ward patients under the supervision of a given Division, except patients with communicable diseases. Most of the primarily nonmedical patients should be examined by a general internist or one serving in this capacity, even though they are to be seen by a specialist (not in the Department of Medicine). It is desirable to have a general internist serve as a coordinator in dealing with many of the patients examined by several specialists.

It is desirable to appoint as head of the major Clinical Laboratories three persons with a Ph.D. and/or an M.D. degree whose activities are in one or another of the following fields: chemistry, microbiology and hematology. These individuals should have the same high-level academic qualifications as other staff members in the medical school, be expected to participate in approximately the same amount of teaching and research as other staff members, and have faculty titles like others (in the basic science or clinical departments) in their respective specialties.

In the next paper,<sup>2</sup> policies dealing with teaching programs are to be presented.

#### ACKNOWLEDGMENT

I am glad to indicate my deep appreciation to the many staff members who gave so freely of their time in responding to a questionnaire that I submitted to them. This material serves as the major basis for this paper.

#### SUMMARIO IN INTERLINGUA

Un questionario, concernite con certe questiones de politica futur pro departimentos de medicina in le areas de administration, instruction, recercas, e cautela de patientes, esseva presentate al chef del departimento de medicina in omne schola medical in le Statos Unite. Un simile questionario esseva inviate a omne membro plenari del personal del departimentos de medicina con le restriction que ille habeva un etate de inter 38 e 50 annos e esseva un membro del Societate American pro le Investigation Clinic e/o del Association de Medicos American. Le responsas al questiones debeva esser formulate in le lumine de certe premissas supponente le disponibilitate de facilitates de character plus o minus ideal. Ben que—naturalmente—differentias de opinion deveniva manifeste e ben que certes del questiones esseva difficile a tractar categoricamente, un serie de punctos pertinente que esseva favorate

per le majoritate del questionatos es presentate infra. Un total medie de 32 membros plenari in le personal del departimento individual de medicina esseva considerate como desirabile per le chefs; und total medie de 25, per non-chefs. Currentemente le total medie es 15. Le numeros medie de specialistas desirate descresceva in le sequente ordine: Internistas general, cardiologos, endocrinologos, neurologos, hematologos, gastroenterologos, respirologos, dermatologos, renologos, microbiologos, rheumatologos, allergiologos, isotopologos, oncologos, geneticistas, nutritionistas, pharmacologos, gerontologos. Multo pauc respondentes favorava un stato departimental pro ulle del correspondente specialitates. Le majoritate del respondentes opinava que omne specialitate representate per un membro plenari del personal deberea esser considerate como un division del medicina e, como tal, deberea gauder de un relativemente alte grado de independentia con respecto al instruction, al recercas, al administration, e al cautela del patientes, providite que illo se pone de accordo con le politicas del departimento, que illo participa in le interprisas cooperatori que es indicate, e que illo adjusta su procedimentos harmoniosemente con le plano general del departimento. In plus, si un specialitate es representate per plus que un sol membro del personal, un de illes debe esser designate como director, capite, o chef de su division. Omne division debe effortiar se a coordinar su activitates con altere divisiones e departimentos.

A generalmente parlar, quando un nove membro del personal es ingagiate como specialista pro un division particular de medicina, il es preferite trovar un medico qui ha completate su periodo de fellow de recerca a un tempora recente plus tosto que un medico al nivello de professor associate, sed il existe distincte exceptiones in iste question.

In caso de competition de varie preoccupationes pro le tempore del chefs, le sequente ordine de prioritate debe esser observate: Administration, instruction, recerca, e le quantitate de tempore dedicate a ille preoccupationes debe sequer le mesme ordine. In le caso de non-chefs, le correspondente ordine deberea esser: Instruction,

recerca, administration. Circa 10 a 15 pro cento del tempore de non-chefs pote esser dedicate a affaires administrative, con le resto dividite plus o minus equalmente inter instruction e recerca. Le chef del departimento es supercargate de deberes administrative. Le suggestiones pro meliorar iste situation consisteva de un o plures del sequentes: Assistentia ab bureaus central, melioration del politicas administrative general, ingagiamento de un assistente functionario executive (qui esserea un medico) e/o un gerente administrative, installation de un super-secretario, assistentia fornite per le chefs del divisiones, e delegation de considerabile grados de responsibilitate al chefs pro lor divisiones individual.

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### CASE REPORTS

# HYDATID CYST OF THE LIVER RUPTURING INTO THE BILE DUCTS: A CASE REPORT DESCRIBING A CHARACTERISTIC TRIAD OF SYMPTOMS\*

By William Antine, M.D.,† and Sheldon P. Rothenberg, M.D., Brooklyn, N. Y.

Although hydatid disease is frequently encountered in Central Europe, Australia, South America and North and South Africa, where sheep, horse and cattle-raising represents an important segment of industry, its occurrence in the United States is comparatively rare. Bockus¹ states that in the slightly more than 500 cases reported as having occurred in this country, 95% have been in persons born in foreign lands, mainly in immigrants from Mediterranean countries. Since the publication of Bockus' work in 1946 there has been an easing of restriction on immigration, and with the increased use of airplane travel it is not unreasonable to suppose that many more cases of echinococcus disease will appear in various parts of this country.

The following report describes a patient with a hydatid cyst of the liver complicated by rupture into the bile ducts. It not only emphasizes some of the difficulties in diagnosis but also describes a triad, previously reported but seldom recognized in this country.

#### CASE REPORT

A 42 year old white male who had emigrated from Italy seven years previously was first seen on January 10, 1956. His chief complaints were weakness and fatigue. He had been well until about five years previously, when, while sitting in his office, his eyes and face suddenly became intensely engorged. He developed a fever; the symptoms subsided in several days. He had then been well for about one year when he experienced an attack of upper abdominal pain, associated with nausea and vomiting but no jaundice. Early in 1955 he had been seized with sharp right upper quadrant pain; he had a fever of 102° F., and his skin became "red and itchy." This was followed by the appearance of jaundice and the passage of dark urine and clay-colored stools. By the end of two weeks all symptoms had cleared. In October, 1955, he had a similar episode and was admitted to another hospital, where a work-up was reported as negative. He was discharged with a diagnosis of viral hepatitis.

Physical examination and a gastrointestinal study consisting of cholecystography, stomach and small bowel x-rays, sigmoidoscopy and a barium enema failed to reveal any abnormalities. The total bilirubin was 0.37 mg.% and the cephalin-flocculation was negative.

<sup>\*</sup> Received for publication September 6, 1957.

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On June 9, 1956, he was seen again because of urticaria, coryza and epigastric pain radiating to the back. At this time the only positive finding was a 2 plus reaction for bile in the urine. One week later the biliuria had subsided.

Two months later the patient had the sudden onset of urticaria associated with severe upper abdominal pain which radiated to the right side and back. There was a slight fever. Examination now revealed marked icterus associated with tenderness and spasm in the right upper quadrant. Bile was again present in the urine.

The patient was admitted to Maimonides Hospital on August 9, 1956. Physical examination revealed a thin, moderately ill man with icteric sclerae and skin. The temperature was 100.4° F. There were tenderness and spasm in the right upper quadrant. The liver edge was palpated two fingerbreadths below the right costal margin, and a 4 to 5 cm. firm round mass was now felt in the epigastrium.



Fig. 1. Cross-section of echinococcus cyst revealing chitinous capsule and daughter cysts.

Laboratory studies revealed a negative urinalysis and blood count. No eosino-philia was noted on any of three occasions. The blood urea nitrogen was 14 mg.%; total protein, 7.3 gm.%, with an albumin of 3.5 gm. and a globulin of 3.8 gm. The prothrombin time was normal; total bilirubin, 8.0 mg.%; cholesterol, 234 mg. total, with 27% free; cephalin-flocculation test, negative; thymol turbidity, 1.5 units; alkaline phosphatase, 17.6 King-Armstrong units, rising to 29.2 units on August 13, 1956. The serum amylase was 143 Somogyi units, and the urine urobilinogen, 3.6 E. U. A flat plate of the abdomen revealed a questionable calculus in the right upper quadrant.

Because of the history of repeated attacks of colic and jaundice, laboratory evidence of biliary obstruction and a palpable mass in the liver, laparotomy was deemed advisable. The preoperative diagnosis was common duct stone or hepatic metastatic neoplasm.

At operation a large, irregular, pinkish white mass occupied about 85% of the

left lobe of the liver and extended into the right lobe. It was cystic in part and at one point, where pierced, was found to contain many small, translucent, pearly white cystic masses measuring 1 cm. in diameter. A diagnosis of hydatid cyst was made and 50 mg. of Phenergan were given intravenously to prevent an allergic reaction.

The common duct and portal structures were dissected out in part and found to be relatively normal in appearance. No stones were palpable in the gall-bladder. The left lobe of the liver was then delivered into the wound and the mass dissected out by sharp and blunt dissection. About 90% of the mass was removed, but a small remnant, measuring about 3½ cm. in diameter, situated at the cephalad end was left behind because of its proximity to the major hepatic ducts and blood vessels. The contents of the remaining cyst were then aspirated. The walls of the cyst were swabbed with 10% formalin, and 2 ml. of formalin were injected into the residual cystic mass and allowed to remain for several minutes. It was then aspirated. Bile-stained fluid was noted emanating from the cyst opening, indicating a communication with the biliary tree.

The postoperative course was uncomplicated except for an initial low grade fever. The patient was discharged three weeks following surgery.

When seen one month later he had no complaints. On further questioning he stated that as a small boy he had frequently visited his grandfather's farm in southern Italy and that his grandfather had had a number of sheep and dogs with which he had come into contact.

The specimen (figure 1) consisted of a grapefruit-sized, multilocular, thick-walled cystic structure measuring 10.5 cm. in diameter. The walls were yellowish gray and measured up to 0.3 cm. in thickness. The interior of the cyst was filled with numerous round cystic structures varying in size from a few millimeters up to 3 cm. in diameter. All the cysts contained water-clear fluid.

Microscopically, the portion of the cyst attached to the liver was composed of a thick, fibrous wall which contained foci of chronic inflammation and foreign-body giant-cell reaction. The hepatic tissue showed portal fibrosis and hyperplasia of the bile ducts. The daughter cysts were composed of lamellated walled cysts which were homogeneous and acellular. A few scolices were seen close to the wall.

#### DISCUSSION

The patient presented the triad of biliary colic, urticaria and jaundice. Lack of familiarity with this symptom-complex resulted in our failure to recognize the disorder preoperatively. This triad had been described by Dew<sup>2</sup> in his classic monograph on hydatid disease, and although it has long been known in endemic areas, its significance has been largely overlooked in the United States.

Dew <sup>2</sup> described anaphylactic phenomena associated with intrabiliary or intraperitoneal rupture of hepatic cysts. The sudden release of antigenic fluid from such cysts into the blood stream may produce symptoms in the cardio-vascular, pulmonary or cutaneous systems. One of Dew's patients developed urticaria, syncope, shock and asthma on several occasions, and at operation was found to have a hepatic cyst with bile-stained contents. Such anaphylactic phenomena have seldom been noted in the North American literature. While most reports mention right upper quadrant pain, jaundice and often roent-genologic evidence of hepatic cysts, very little note has been made of the allergic reactions. In the review of Poore et al.<sup>3</sup> from the Mayo Clinic, 40 case records of patients with hydatid cysts, primary in the liver, were studied. Of their 40 patients, 14 (35%) gave a history of severe biliary colic at some time in the

past. Thirteen of the 14 also had a history of jaundice with one or more of their attacks of biliary colic. None of the 40 patients had had urticaria or asthma. Similarly, reports by Wilensky, Deeds and Gennaro failed to note anaphylactic phenomena. The most recent reference to the triad is to be found in the report of Atlas and Kamenear. In 1952 they reported two cases of hydatid disease with rupture into the biliary ducts. However, only one of their cases had an associated urticaria. They called the syndrome "pseudocholelithiasis," to differentiate it from true biliary colic. They pointed out the importance of anaphylactic or urticarial reactions and eosinophilia in the diagnosis. The triad may be incomplete, with one or another of its features being absent at various times. It seems likely that more careful history taking in patients suspected of having hepatic hydatid cysts would reveal a higher incidence in the past of urti-

caria and vague abdominal pains.

A brief review of the pathogenesis of this disease may help to explain some of the variations encountered.8 Man is not a natural intermediate host of Taenia echinococcus, but rather an accidental one in whom further progression of the life cycle does not take place. Infestation occurs by ingestion of the ova through contamination of either food or fingers. Most cases are contracted in childhood. The embryo is hatched in the stomach and bores its way through this viscus, or the upper part of the small intestine, into the radicles of the portal system, which carry it to the liver. The host tissue produces an inflammatory reaction around the developing cyst which finally becomes the adventitia of the cyst wall. According to Dew,2 small biliary channels persist in this area, and patent ducts may be discovered in close proximity to the cyst itself. The cyst continues to increase in size by the elaboration of fluid and the deposition of laminated hyaline material around it. The rate of growth is variable, depending mainly upon the character of the surrounding tissue. Most cysts give rise to no symptoms until they are 6 to 8 inches in diameter. This may take 20 to 30 years. Hepatic hydatid cysts may produce symptoms by pressure or suppuration, or by rupture into the peritoneal cavity, lung or biliary system.

It is surprising that the occurrence of anaphylactic reactions is not more common with intrabiliary rupture, since 90 to 95% of all cases of hydatid disease show a positive skin test, indicating that the patient has been sensitized to the hydatid antigen. The occurrence of such reactions probably depends upon the antigenic hydatid fluid getting directly into the blood stream through small open vessels adjacent to the site of rupture. Liberation of a small amount of fluid may produce only minor sensitization reactions. In those cases where a large amount of fluid is liberated the reactions may be more severe. Blocking of the bile ducts by liberated daughter cysts, or by debris from the cyst wall, is responsible for the jaundice. The rupture of the cyst produces the right

upper quadrant pain.

Various diagnostic aids have been utilized. Eosinophilia is present in 25% of the cases.<sup>2</sup> Precipitin and complement fixation tests are available and are positive in 56 to 60% of patients before their first operation.<sup>9</sup> With recent rupture or suppuration, Dew states that they become positive in 95 to 100% of cases. Casoni's skin test, using pooled hydatid fluid from uncomplicated cysts of sheep, is a simple and useful diagnostic procedure. An early wheal reaction

occurs in 90 to 95% of cases. Suppuration or rupture may be responsible for a negative skin test for a variable time after its occurrence.

#### SUMMARY

A patient has been reported who had the characteristic triad of right upper quadrant pain, urticaria and jaundice, resulting from T. echinococcus infestation.

A brief review of the literature and a description of the pathogenesis of this disease have been outlined.

#### SUMMARIO IN INTERLINGUA

Morbo hydatidic non es commun in le Statos Unite. Le majoritate del casos reportate in iste pais ha occurrite in immigrantes ab paises mediterranee. Per consequente, cystes hydatidic del hepate es rarmente prendite in consideration in le diagnose de obscur dolores abdominal, mesmo in casos in que illos es associate con jalnessa o con le presentia de un massa in le hepate. Quando tal cystes rumpe e se discarga a in le vias biliari, le resultante colica es usualmente attribuite a calculos in le vesica o le commun ducto biliari.

Es describite un patiente qui exhibiva un triade characteristic de symptomas. Ille esseva un italiano qui habeva arrivate in iste pais septe annos previemente. Ille se habeva semper trovate ben, usque cinque annos ante su currente maladia quando ille habeva un subitanee episodio de sever urticaria e febre que subsideva intra alicun dies. Postea ille se trovava ben durante un anno. Alora ille habeva un attacco de dolor in le quadrante dextero-superior, con febre, urticaria, e jalnessa. Iste symptomas durava duo septimanas. Plure menses plus tarde un simile episodio requireva su hospitalisation. Un studio complete del caso resultava in un reporto negative. Le diagnose al tempore del dimission ab le hospital esseva hepatitis virusal. Episodios additional del mesme typo duceva al ultime hospitalisation del patiente. Ille habeva jalnessa, e un massa deveniva palpabile in le epigastrio.

A causa del documentation laboratorial de jalnessa obstructive, laparotomia exploratori esseva interprendite. Esseva constatate que le patiente habeva un cyste hydatidic con rupturation a in le vias biliari.

Iste patiente presentava un triade diagnostic que consisteva de colica biliari, urticaria, e jalnessa. In le presentia de un tal triade de symptomas, il es semper recommendabile prender in consideration le possibilitate de cyste hydatidic con rupturation a in le vias biliari. Tests de laboratorio que va possibilimente esser de adjuta in confirmar le diagnose es le test pro eosinophilia, le tests de precipitina e fixation de complemento, e le test cutanee de Casoni.

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## CASE OF A DIABETIC WITH A KIMMELSTIEL-WILSON SYNDROME AND A NORMAL GLUCOSE TOLERANCE \*

By WILLIAM S. COLLENS, M.D., F.A.C.P., Brooklyn, N. Y., JOSEPH N. SILVERSTEIN, M.D., Aberdeen, Maryland, and Gerald B. Dobkin, M.A., Brooklyn, N. Y.

This paper reports a patient with diabetes and a Kimmelstiel-Wilson syndrome whose capacity to handle carbohydrate was normal by standard glucose tolerance tests. Although these tests were normal by both the oral and the intravenous routes, the first sign of any abnormality was seen when the patient was exposed to stress by both steroids and infection.

#### CASE REPORT

A 42 year old Jewish male first came under observation at the Maimonides Hospital in July, 1954. He was admitted to the surgical service for the treatment of an abscess of the breast. The urine at this time showed 3 plus glycosuria, 4 plus acetone and 2 plus albumin; the specific gravity was 1.033. He stated that he was first found to be diabetic in 1942 and was treated with a reducing diet. He had never received any insulin. In the hospital he was treated with a restricted diet and 20 units of insulin a day during the time of his surgical management.

The patient was re-admitted to the hospital on July 10, 1956, for a four-month stay. During this period he was operated upon for a carbuncle on his neck. He was also treated for gangrene and cellulitis involving the left fifth toe. The toe was amputated and he made an uneventful recovery after treatment with intensive antibiotic therapy. His urine specimens during this period revealed the presence of traces of sugar, 4 plus albumin and many granular casts; the specific gravity was 1.010. His fasting blood sugar on July 10, 1956, was 201 mg.%. He was treated with sporadic doses of insulin during this period.

The patient was admitted to the hospital for the third time on December 22, 1956, for the treatment of sciatic neuritis and hypertrophic osteoarthritis. At this time his urine specimens revealed no sugar, but contained 4 plus albumin and granular casts. His fasting blood sugar was 115 mg.%; blood urea nitrogen, 13. mg.%; uric acid, 7.5 mg.%.

He reëntered the hospital on January 29, 1957, for an evaluation of his medical status. His chief complaints were weakness, edema of his lower extremities and blurring of vision. These symptoms had developed in the last two months. Physical examination revealed an obese individual in no acute distress. Blood pressure was

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180/100 mm. of Hg. His eyegrounds showed classic diabetic retinopathy, with numerous hard, sharply demarcated exudates, many microaneurysms and several hemorrhages in both fundi (figure 1). There was evidence of hypertrophy of his left ventricle, which was corroborated by radiologic study. The peripheral pulses were present. There was marked reduction in transmission of vibratory sense impulse. Laboratory data: Urine: albumin, 4 plus; sugar, negative; specific gravity, 1.007. Granular casts were present, but doubly refractile bodies were not found.

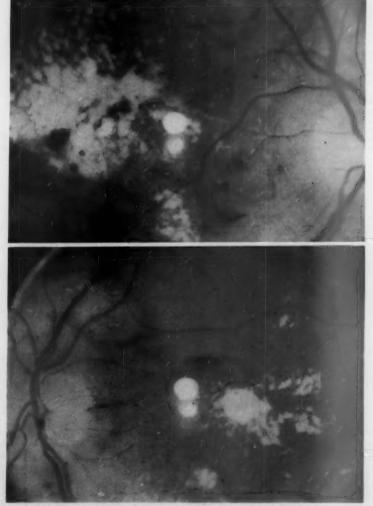


Fig. 1. Fundus photograph. (above) Right eye. (below) Left eye. Note extensive, sharply demarcated exudates, hemorrhages and microaneurysms in both fundi. Note also sharp disc margins.

TABLE 1

	1/30/57	2/4/57	2/12/57	3/13/57	3/17/57	3/18/57	3/19/57	3/21/57	3/27/57
F. Bl. Sugar mg.%	102	87		93					
B. S. 2 hrs.		82				87			
BUN mg.%	22	26		31	28			31	33
T P gm.% Alb. Glob.	5.7 2.2 3.5	6.6 2.9 3.7	6.6 3.2 3.4	6.0 2.8 3.2			-:::		
Ict. Index Tot. Cholest. mg.% Ceph. Floc.	5 267 neg.		338	324					
Thy./Turb. Alk. Phos. CO <sub>2</sub>	5.4	29.4		30.5	29.8			20.6	
mEq. Chlorine Sodium		109 147		103 142	107 138		102	101 142	
Potassium Calcium Phosphorus		5.7		5.2	5.9		5.9	5.9	10.1

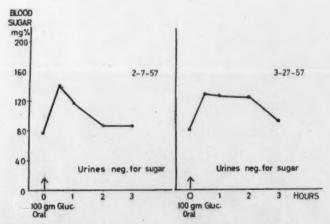


Fig. 2. Two oral glucose tolerance tests. Both showed normal curves.

TABLE 2

2/7/57	Blood	Urine	3/27/57	Blood	Urine
Fasting	79 mg.	.0	100 cm clusoso	80 mg.	0
100 gm. glucose	140 mg.	0	100 gm. glucose	130 mg.	0
1 hour	117 mg.	. 0		126 mg.	0
2 hours	87 mg.	0		124 mg.	0
3 hours	86 mg.	0		92 mg.	0.

TABLE 3

	A JEDDE		
3/26/57	12 midnight 6 a.m.	62.5 mg. cortis	
		Blood Sugar	Urine Sugar
8 a.m. Fasting	g cose given p. o.	105 mg.	0
4 hour	9	174 mg.	0
1 hour		160 mg.	0
2 hours		145 mg.	0
3 hours		120 mg.	0

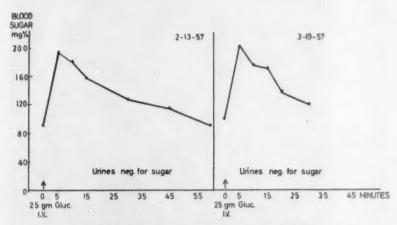


Fig. 3. Two intravenous glucose tolerance tests showing normal curves.

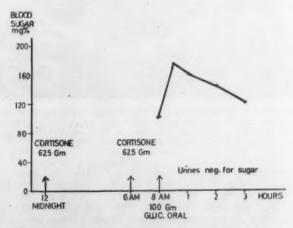


Fig. 4. Glucose tolerance test after stress with cortisone. Note slight delay in return of blood sugar to normal level.

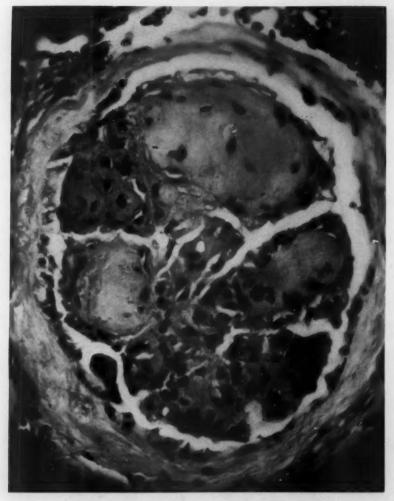


Fig. 5. Renal biopsy. Glomerulus of kidney, showing nodular hyaline masses arranged mainly at periphery of the glomerulus opposite the entrance of afferent arteriole. There is marked capsular fibrosis. Lesion characteristic of Kimmelstiel-Wilson disease.  $\times$  500. (Interpretation by Dr. A. Kantrowitz, pathologist, Maimonides Hospital.)

Further laboratory studies are presented in table 1. His blood sugar on admission was 102 mg.%, and the blood urea nitrogens were, on various occasions, 22, 26 and 21 mg.%. The total serum protein ranged between 5.7 and 6.6 gm.%. Albumin was 2.2 to 2.9 gm., globulin, 3.5 to 3.7 gm. The cholesterol determinations ranged between 267 and 333 mg.%; esterification was normal. Other laboratory data were as follows: a normal icterus index, normal alkaline phosphatase (5.4 King-Armstrong units), a normal peripheral blood count and a sedimentation rate of 38 (Wintrobe).

Two oral glucose tolerance tests were normal, as shown in table 2 and figure 2. The performance of an intravenous glucose tolerance test with the injection of 50 c.c. of 50% glucose gave normal results on two occasions (figure 3). It was obvious from these tests alone that a definitive diagnosis of diabetes mellitus could not be made. To determine whether the patient was still a diabetic, a stress test was performed by the technic of Conn and Fajans, with results shown in table 3 and figure 4.

A renal biopsy performed by the resident, Dr. Marvin Kranis (figure 5), showed the presence of the characteristic lesions of a diabetic nephropathy as described by Kimmelstiel and Wilson.<sup>2</sup>

#### DISCUSSION

The interesting feature presented by this patient was the disappearance of the diabetes as far as its recognition by his capacity to utilize glucose was concerned. In spite of this he developed a profound form of unequivocal diabetic nephropathy and retinopathy as documented by renal biopsy and fundus photographs. It would appear from this that the disturbance in carbohydrate metabolism which occurs in diabetes as a result of a disordered insulin function may be independent of the mechanism responsible for the nephropathic and retinopathic changes often seen in the diabetic.

Zubrod et al. have shown that in patients dying with nephropathic kidneys the diabetes usually assumes a milder form.<sup>3</sup> They also observed that these patients had never previously experienced bouts of uncompensated acidosis. These observations, however, were not confirmed by Runyon.<sup>4</sup> Nevertheless, it has been commonly observed that the development of a Kimmelstiel-Wilson syndrome in life can be found in both mild and severe diabetics.<sup>5</sup>

It would appear that the control of the diabetes to the extent which this patient manifested did not seem to protect him against the development of the Kimmelstiel-Wilson syndrome. This does not in itself justify the argument of those who maintain that, since the degree of the control of the diabetes plays no part in halting the advent of nephropathic complications, and since these changes seem to be the inexorable sequelae of diabetes, strict control of the diabetes is of no value. There are many advantages to be derived from the proper regulation of the diabetes, such as those that go with reconstituting physiologic consumption of carbohydrate, improving the nutritional state, preventing undue loss of electrolytes with dehydration, and preventing pruritus vulvae.

There is probably some other mechanism in the body completely divorced from a disturbance in insulin metabolism which is participating in the production of nephropathy, retinopathy and even neuropathy. We have demonstrated that the transmission of vibratory sense impulse through the extremities is much more pronouncedly impaired in patients who have a proteinuria than in diabetics free from proteinuria.<sup>6</sup> Root has even indicated that patients who develop this syndrome have a triopathy consisting of nephropathy, retinopathy and peripheral neuropathy.<sup>7</sup> We have also noted that diabetics with proteinuria show a more profound increase in the concentration of serum lipoproteins, particularly of the SF 12-20 class, as compared with diabetics who are free from proteinuria.<sup>8</sup> It is possible that there is a common denominator unrelated to insulin function which plays a part in producing these three complications in

diabetics. Certainly a patient with what would appear to be a normal insulin function who yet develops nephropathic and retinopathic changes would indicate that there are two separate systems operating in the diabetic, and that a disturbance in the function of insulin as it affects the metabolism of carbohydrate and fat is only one facet of the over-all picture of diabetes mellitus.

#### Conclusions

A patient with diabetes mellitus is presented in whom the manifestations of diabetes disappeared. Despite this, a profound nephropathy (Kimmelstiel-Wilson kidney) and diabetic retinopathy developed. Diabetes could be detected only under adrenal stress.

#### SUMMARIO IN INTERLINGUA

Es describite le caso de un patiente mascule qui disveloppava manifestationes de diabete mellite al etate de 30 annos. A ille tempore, le patiente habeva marcate grados de glycosuria e hyperglycemia. Ille esseva tractate solmente per dieta a reduction de peso corporee. Dece-duo annos plus tarde, hospitalisate pro un abscesso pectoral, ille primo recipeva insulina durante un certe periodo de tempore. Duo annos plus tarde ille esseva re-hospitalisate con un carbunculo e cellulitis del quinte digito sinistro-pedal. Le nivello del sucro sanguinee in stato jejun esseva 201 mg pro cento. Solmente tracias de sucro esseva notate in le urina. Ille recipeva insulina durante un certe periodo. Dece-cinque annos post le discoperta original de su diabete, le patiente esseva hospitalisate de novo. Ille exhibiva signos definite de un plenmente disveloppate syndrome de Kimmelstiel-Wilson, characterisate per proteinuria, cylindros granular in le urina, classic retinopathia diabetic, e hypertensive morbo vascular. Biopsia renal revelava le presentia de depositos hyalin characteristic de glomerulosclerosis intercapillar. Durante iste sojorno al hospital le urina se monstrava libere de sucro; al tempore del admission al hospital le sucro del sanguine mesurava 102 mg pro cento. Duo tests del tolerantia pro glucosa oral se monstrava normal, e un test de stress a cortisona revelava signos non plus que suggestive de diabete in le curva del sucro de sanguine.

Es discutite le mechanismo del disveloppamento del syndrome de Kimmelstein-Wilson.

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#### PRIMARY HEMANGIO-ENDOTHELIOMA OF THE HEART\*

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It is the purpose of this paper to present the first malignant hemangioendothelioma of the heart to be diagnosed ante mortem by thoracotomy and frozen section, and the twelfth such case to be reported in the literature.

The incidence of primary cardiac tumors in necropsy studies by Straus and Merliss was estimated to be 0.0017%, as compared to 0.24% to 6.45% for metastatic cardiac tumors.2-5 Lymburner 6 encountered four benign primary tumors in a series of 8,550 consecutive autopsies. From his series of 329 cases of primary cardiac tumors, Mahaim 7 found 87 to be malignant. From a study of 20,337 autopsies Whorton 8 in 1949 found three primary cardiac tumors, two benign and one a reticulum cell sarcoma. These added cases of primary malignancy increased the total to 100, nine being rhabdomyosarcoma. In 1955 Cheng and Sutton added a case diagnosed by angiocardiography, reviewed the literature, and raised the total reported cases of primary sarcoma of the heart to 135.

Primary hemangio-endotheliosarcoma of the heart is exceedingly rare. The 11 cases previously described have been diagnosed principally at autopsy, one by biopsy of bone metastasis, one by demonstrating tumor cells in the pericardial fluid, and one by angiocardiography 9-17 (table 1).

According to Legg and Fitch, 18 who have classified vascular tumors as to histogenetic range, the hemangio-endotheliosarcoma would be the genuine angioma or true hemangio-endothelioma.

Kastl 19 is of the opinion that hemangio-endothelioma may arise in practically any organ of the body, showing no special predilection.

The male-to-female ratio is 7:4. The racial occurrence is predominantly Caucasian, two cases having been described in the Negro. The age incidence is from the third to the seventh decades. This disease has not been reported in a patient younger than 25 years, and in only one case older than 45 years.

Prognosis is invariably poor, death usually resulting within a few months of discovery.

No satisfactory treatment for malignant hemangio-endothelioma has as yet been devised. Roentgen radiation is of no definite benefit.

No characteristic clinical picture of primary cardiac tumors, especially in the early course of the disease, is recognized.

#### CASE REPORT

A 38 year old white female waitress entered the Highland Baptist Hospital in Birmingham on January 7, 1957, complaining principally of cough, generalized fatigue and midchest pain of approximately two weeks' duration. The illness was actually thought to have begun in July, 1956, at which time she had been hospitalized

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by another physician because of an "enlarged heart, weak spells, anemia and fluid on the lungs." She was told that she had congestive heart failure. A digitalis preparation and diuretics were prescribed but gave only temporary help. During the interval from July, 1956, until hospital admission in January, 1957, she apparently improved somewhat, as she was able to continue her regular job as a waitress.

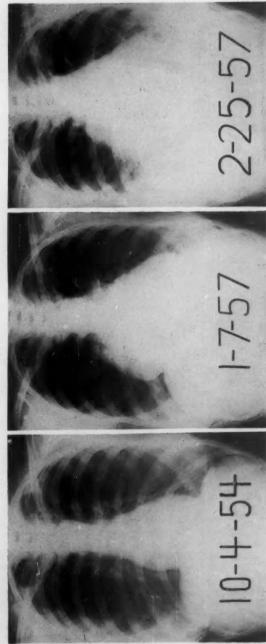
Past history and family history were noncontributory.

Physical Examination: The patient was a 38 year old female in no apparent distress but appearing to be moderately chronically ill. The significant points of the

TABLE 1

Authors	Diagnosis	Site in Heart	Metastases	Race Sex	Age	Remarks
Redtenbacher <sup>10</sup> 1889	Autopsy	Pericardium but communicat- ing with right ventricle				
Hewer and Kemp <sup>11</sup> 1936	Autopsy	Right atrium	Lungs, bronchial lymph nodes, mesentery, vertebrae	White Female	62	Also benign cavernous hemangiomata of liver and esophagus
Gross and Englehart <sup>12</sup> 1937	Autopsy	Left atrium	None	White Female	45	Polypoid lesion, also rheumatic heart dis- ease and mitral stenosis
Choissier and Ramsey <sup>13</sup> 1939	Autopsy	Right atrium	Pericardium, mediastinum, pleura, liver	White Male	26	Right hemothorax. Reported Kaposi's disease. No skin lesions
Choissier and Ramsey <sup>18</sup> 1939	Autopsy	Right atrium	None	White Male	30	Hemopericardium. Bi- lateral hemothorax. Reported as Kaposi's disease. No skin lesions
Glassy and Massey <sup>15</sup> 1950	Autopsy	Probably right atrium	None	White Male	26	
Tacket et al.14 1950	Tumor cells in pericardial fluid	Right atrium	Lungs	Negro Female	45	Polypoid projection into tricuspid valve
Blanchard and Hethrington <sup>16</sup> 1952	Autopsy	Right atrium	Lungs, liver, right adrenal	White Male	25	
Blanchard and Hethrington <sup>16</sup> 1952	Biopsy of bony me- tastasis	Right atrium	Lungs, liver, bones	White Male	33	Direct erosion of sternum
Cheng and Sutton <sup>9</sup> 1955	Angiocardi- ography	Right atrium	Liver	Negro Male	45	
Groom <sup>17</sup> 1956	Autopsy	Right atrium	Lungs, liver, adrenals, ribs	White Male	38	
Crenshaw et al. 1957	Thoracotomy by frozen section	Right atrium	Lungs, liver	White Female	38	Direct extension through sternum, polypoid in part

examination were confined to the chest. The point of maximal impulse of the heart was felt at the midclavicular line in the fifth intercostal space. The left border of the heart on percussion was 9 cm. to the left of the midsternal line; the right border of heart dullness seemed to be extended slightly. The cardiac rate was 120, with a sinus arrhythmia. Grade 1 systolic and grade 3 diastolic murmurs were heard along the left sternal border, varying with the respiratory cycle. A grade 1 presystolic mitral murmur with slight roughening of the first mitral sound was detected. (In 1954 a grade 2 systolic mitral murmur and grade 1 basal systolic murmur were



Serial x-rays showing cardiac enlargement, particularly of the right heart shadow, and in the postoperative films small infiltrative lesions within the lungs, interpreted as metastatic tumor. FIG. 1.

reported.) Examination of the lungs revealed a few transient coarse râles in the right base.

X-ray: Fluoroscopic examination and multiple chest films showed a large tumor mass well circumscribed and lobulated in appearance, apparently arising from the right side of the mediastinum or directly from the heart itself. The most likely possibilities were thought to be either a mediastinal mass or a cardiac tumor. Previous x-ray studies of the digestive system, including gall-bladder, upper gastrointestinal tract, and colon, were considered to be normal. An x-ray of the chest taken in October, 1954, showed a normal heart and lungs.

Electrocardiogram: The routine 12-lead tracing showed a rate of 130, with sinus arrhythmia and decreased amplitude of the T waves throughout.

Clinical Course: Because of the diagnostic possibilities suggested by the x-ray examination, exploratory thoracotomy was performed on January 14, 1957.\* When the pleural space was entered a large, semisolid mass was found which was attached



Fig. 2. Tumor eroding sternum and growing in the subcutis of the chest wall.

to the mediastinal portion of the right lung. The mass was freed, and there appeared to be many hemangiomatous vessels in the tumor. An obliterative type of pericarditis was found upon opening the pericardium. The mass was of such proportions that it was impossible to identify any of the right auricle or ventricle. The dissection was carried out so that the thoracic aorta, superior vena cava and all vessels from the right lung could be well visualized. A large purse-string suture was then placed around that portion of the mass which was overlying the auricle. This was incised, and when a finger was inserted it was found that this mass was all tumor, and that it was impossible to insert the finger into the auricle itself. A firm mass was palpable but not visualized in the right wall of the heart at the junction of the auricle and right ventricle. This mass was biopsied and was reported as malignant hemangio-endothelioma. Because of this finding, together with the extensive invasion into the heart wall, no further surgery was thought to be indicated.

The postoperative course was uneventful, and the patient was able to leave the

<sup>\*</sup> Performed by Dr. Charles Donald and Dr. O. W. Clayton, Staff, Highland Baptist Hospital, Birmingham.



Fig. 3. Tumor growing in the heart,



Frg. 4. Multiple small metastases in lung.

hospital by automobile for her home in Mississippi after approximately two weeks. One of us (W. F. C.) followed the case to its termination in her Mississippi home.

Necropsy Report: \* The heart was irregular in shape, greatly enlarged and adherent to the overlying chest plate. The weight of this shaggy cardiac mass was 630 gm. The right atrium was almost completely replaced by a spongy, reddish brown hemorrhagic neoplasm which extended beyond the confines of the heart to erode the overlying sternum and invade the muscles, subcutis and skin of the chest wall (figure 1). This invasion of the chest wall produced a bluish, bulging tumor mass underlying the skin. Within the right atrium the neoplasm presented as a reddish brown, partly necrotic polypoid mass arising from the lateral aspect above the tricuspid opening. The tumor mass in general was of such size and distribution

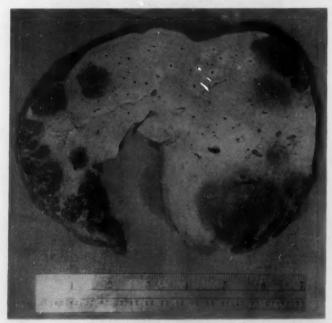


Fig. 5. Metastases in liver.

as to compress severely the superior vena cava, the pulmonary artery and the left atrium. The inferior vena cava, the aorta and the pulmonary veins did not appear to be directly affected. Figure 2 shows a section of the heart viewed from the left side, but does not give a true picture of the whole tumor mass, which was of much greater size.

Both lungs were heavy (right lung, 720 gm.; left, 620 gm.) and reddish in color, and showed pneumonic consolidation. There were extensive fibrous adhesions of the pleura. The cut surface of both lungs showed scattered small hemorrhagic nodules which were most prominent near the diaphragmatic surface of the left lower lobe. Figure 3 is a representative slice of the lung showing the hemorrhagic tumor nodules.

<sup>\*</sup> Autopsy was limited to an examination of the heart, lungs, chest plate, liver and spleen.

The liver was large, weighing 1,900 gm. The surface was studded with multiple raised, blue-black tumor masses, the largest measuring 4.5 cm. in diameter. The cut surface (figure 4) showed multiple hemorrhagic areas of neoplasm, arranged predominantly under the capsule and affecting both right and left lobes.

Histologically, the neoplasm showed a vascular, spongelike or sinusoidal arrangement with some papillary configuration (figure 5). Vascular endothelium appeared to be the proliferating tissue, hence the diagnosis hemangio-endothelioma. Many of the vascular spaces were thrombosed. Mitotic figures were moderately abundant.

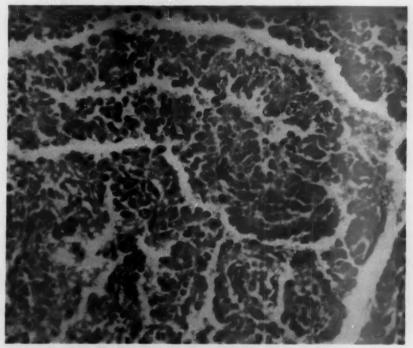


Fig. 6. Malignant hemangio-endothelioma of heart. × 400.

The tumor presented an essentially similar picture in heart, lungs and liver. The lungs were also the site of confluent lobular pneumonia.

#### DISCUSSION

Malignant hemangio-endothelioma is a rare tumor of the heart. A review of the literature reveals that only 11 cases have been reported to date, and the salient features of these are summarized in table 1. The present case is therefore the twelfth to be described. Diagnosis has previously been made during life, however, in only three instances. Blanchard and Hethrington, 16 guided by previous personal experiences in a similar case, have made the diagnosis on biopsy of a metastasis to bone. Cheng and Sutton 9 have made the diagnosis

of sarcoma of the heart by angiocardiography, the exact diagnosis having been established by subsequent autopsy. Tacket et al. have reported finding malignant cells in pericardial fluid in a case later proved to be malignant hemangioendothelioma. The case here reported, however, is the first of this kind to have been diagnosed at thoracotomy by frozen section.

Certain features of malignant hemangio-endothelioma are common to sarcomata of the heart in general. In 11 of 12 instances the neoplasm arose in the right side of the heart, and in 10 of these cases was situated in the right atrium. The eleventh (Redtenbacher's 10), the oldest in the literature, was described as a tumor of the pericardium communicating with the right ventricle, but very possibly the ventricle was the primary source.

Metastatic spread has occurred to the following: lungs, liver, bones, adrenals, lymph nodes and mesentery. Direct invasion of the pericardium, pleura and chest wall has also been described, together with hemopericardium and hemothorax. It is also of interest that Gross and Englehart 12 and Tacket 14 and others describe part of the neoplasm as being polypoid, projecting into the tricuspid valve; this was also seen in our case. This may simply be a feature of intracavitary growth, with moulding by the contractile pressures of the heart.

The diagnosis of this case as simple "congestive heart failure" was immediately questioned upon the initial examination, for the patient was seen to be lying supine in bed without evidence of dyspnea, edema, hepatomegaly, venous engorgement or significant râles. Her response to digitalis and diuretics was not that seen in congestive failure. Consequently, other causes were sought for the origin of the cardiomegaly. A comparison of heart size on hospital admission in January, 1957, with that in October, 1954, further demonstrated conspicuous changes in the right portion of the silhouette; this change in configuration was thought to result from a mediastinal mass adherent to the right wall of the heart, or from a cardiac neoplasm. Further diagnostic studies showed no detectable evidence that the lesion was metastatic in origin, such as the hemangio-endotheliosarcoma of the heart which originated in the ileum, described by Grayson.<sup>20</sup>

#### SUMMARY

1. A report is presented of a case of primary malignant hemangio-endothelioma of the heart. This is a rare cardiac tumor, and our report is believed to be the twelfth such case in the literature, and the first to be diagnosed ante mortem by means of thoracotomy with frozen section.

2. The available literature concerning this disease is briefly reviewed.

#### SUMMARIO IN INTERLINGUA

Es reportate un caso de primari hemangio-endothelioma maligne del corde. Illo pare esser le dece-secunde tal caso reportate in le litteratura e le prime diagnosticate ante morte per medio de thoracotomia a section congelate. Le previe 11 casos esseva diagnosticate principalmente al necropsia, un per biopsia de metastases ossee, un per demonstration de cellulas tumoric in le liquido pericardial, e un per angiocardiographia. Nulle satisfacente therapia existe, e le prognose es invariabilemente pauco favorabile. Le uso de radios X es sin beneficio definite. Nulle characteristic tableau clinic de primari tumores cardiac es recognoscibile. Isto vale specialmente durante le prime phases del morbo.

Un femina de racia blanc de 38 annos de etate esseva hospitalisate le 7 de januario 1957 con le gravamines de tusse, fatiga generalisate, e dolores thoracocentral de circa duo septimanas de duration. In julio 1956 illa habeva essite tractate a un altere hospital pro un condition alora considerate como congestive disfallimento cardiac.

Le examine physic monstrava un frequentia cardiac de 120, con un arrhythmia sinusal. Le examine uoroscopic e multiple roentgenogrammas thoracic revelava un extense massa tumoric, de apparentia ben circumscripte e lobulate, que pareva haber su base al latere dextere del mediastino o directemente in le corde. Esseva opinate que le plus plausibile diagnoses possibile esseva un massa mediastinal o un tumor cardiac. In octobre 1954, un roentgenogramma thoracic habeva indicate que le corde e le pulmones esseva normal. Le electrocardiogramma, con registration routinari a 12 derivationes, monstrava un frequentia de 130, con arrhythmia sinusal e reduction del amplitude in le undas T in omne casos.

Thoracotomia exploratori esseva effectuate. Post penetration in le spatio pleural, un grande massa semi-solide esseva trovate attachate al portion mediastinal del pulmon dextere. Le tumor pareva continer multe vasos hemangiomatose. Le proportiones del massa esseva tal que il esseva impossibile identificar le auriculo o le ventriculo dextere. Biopsia del massa produceva le verdicto de hemangio-endothelioma maligne. Ab le puncto de vista histologic, le neoplasma monstrava un structura vascular de character spongiose o sinusoide, con un certe grado de configuration papillar. Le endothelio vascular consisteva apparentemente de histos proliferante, lo que justificava le diagnose de hemangio-endothelioma. Multes del spatios vascular esseva thrombotic. Esseva notate un abundantia moderate de figuras mitotic. Le patiente moriva approximativemente cinque menses post que thoracotomia habeva establite le diagnose del lesion, i.e. circa 11 menses post le apparition del symptomas thoracic. Al necropsia, le tumor presentava essentialmente le mesme configuration in corde, pulmones, e hepate. Studios additional revelava nulle prova que le lesion esseva de origine metastatic.

Es presentate un breve revista del litteratura concernite con iste morbo.

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# CUSHING'S SYNDROME AND THE GUILLAIN-BARRÉ SYNDROME \*

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## INTRODUCTION

The Landry-Guillain-Barré syndrome has been described as a polyradiculoneuropathy which may affect either sensory or motor function and may extend into the central nervous system.¹ The outcome is dependent upon the degree of involvement of the respiratory and cardiovascular centers. Changes in the cerebrospinal fluid protein, and albuminocytologic dissociation, are regarded as being incidental to the disorder. The severe cases have a guarded prognosis, and mortality figures of 12 to 42% have been reported.²,³ The etiology of the syndrome has never been conclusively established, but toxic, infectious and allergic hypotheses have been proposed. The disorder represents a treatment problem because no specific therapy has been found. Since 1952 the efficacy of ACTH and cortisone has been reported.³-10, ²8-28 The basis of this therapy has been the treatment of the neurologic illness as an allergic manifestation. In view of the emergence of ACTH and cortisone as therapy for the syndrome, we wish to report a case of coexistent Guillain-Barré syndrome and Cushing's syndrome where the endocrinopathy and the neurologic disorder coexisted for

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over six months. This seemingly paradoxic combination of syndromes is the fourth reported since 1955.

#### CASE REPORT

A 30 year old white married female teacher was referred to Duke Hospital in

November, 1956, for evaluation of Cushing's syndrome.

In May, 1955, the patient had first experienced the gradual onset of bilateral lower extremity weakness, paresthesias, numbness and loss of sensation. In July, 1955, she had undergone a total thyroidectomy because of a two-year history of nervousness, palpitations and an enlarging goiter. During this hospitalization the neurologic deficit was noted. The patient's weight was 140 pounds and her blood pressure was 200/130 mm, of Hg. She was discharged on vitamin B<sub>12</sub> and Ansolysen. Following discharge the patient developed a persistent facial fullness and began to gain weight. She had crying spells, depressive episodes and decreased libido. Her neurologic illness became progressively more disabling, and she reëntered the hospital in September, 1955. In the hospital she complained of severe vertex headaches. Her blood pressure was 230/180 mm. of Hg. The fundi revealed bilateral papilledema, hemorrhages and exudate.

There was marked symmetric weakness involving the upper and lower extremities and the trunk, maximal in the lower extremities. There were marked impairment of all modalities of sensation and complete deep tendon areflexia. Hemoglobin was 16.1 gm.%. A lumbar puncture revealed a pressure of 420 mm. water and xanthochromic fluid. There were five white blood cells and 944 mg.% protein. A diagnosis of Guillain-Barré syndrome was made, and the patient was discharged to the care

of one of us (C. T. J.) on vitamin B12.

The extremity weakness and sensory loss persisted for almost a year. There was gradual subsidence of all symptoms of the polyneuritis during this time. However, during this year the patient's hypertension persisted and she underwent marked physical and emotional changes. She developed a ravenous appetite and attained a weight of 180 pounds. She had frequent crying spells, depressive episodes and a loss of libido. Her weight gain was manifest as a neck and trunk obesity, with thin extremities. She demonstrated facial plethora, oily skin, hirsutism and acne. Her abdomen revealed a masculine hair distribution and purple striae. She had severe vertex headaches almost constantly. The presumptive diagnosis of Cushing's syndrome was made and the patient was referred to Duke Hospital, where the physical findings were confirmed. The fundi at this time showed only arteriolar narrowing. Neurologic examination was without abnormality. A number of studies were done in the evaluation of the endocrinopathy. Hemoglobin, 18.2 gm.%; hematocrit, 55%; fasting blood sugar, 118 mg.%; cholesterol, 252 mg.%; nonprotein nitrogen, 37 mg.%; sodium, 147 mEq./L.; chloride, 101 mEq./L.; potassium, 4.3 mEq./L.; carbon dioxide, 34 mEq./L. Phènolsulfonphthalein excretion was 40% in two hours. An electrocardiogram was read as left ventricular hypertrophy. Skull x-rays were normal; chest films showed a moderate cardiomegaly. Urinary steroid studies showed both 17-hydroxycorticoids and 17-ketosteroids to be elevated on control days, and to become abnormally high after ACTH (17-hydroxycorticoids, 18.6 mg./24 hours; 22.6 mg./24 hours; after ACTH, 46.4 mg./24 hours. 17-ketosteroids, 17.9 mg./24 hours; 24.7 mg./24 hours; after ACTH, 38.1 mg./24 hours).

These findings were felt to be consistent with a diagnosis of Cushing's syndrome. In December, 1956, the patient underwent a bilateral adrenalectomy. No adenomas were found. The left adrenal weighed 9.5 gm. and the right 13.0 gm. She was discharged to the care of her physician (C. T. J.) on cortisone therapy, and has

shown gradual improvement.

It was evident that the patient was afflicted simultaneously with the Guillain-Barré syndrome and Cushing's syndrome. The neurologic disorder remained in

evidence for at least six months after the onset of the clinical manifestations of Cushing's syndrome.

## DISCUSSION

The occurrence of a Guillain-Barré syndrome in conditions associated with high levels of endogenous or exogenous steroids is known.

Two cases of Cushing's syndrome and Guillain-Barré syndrome have been reported from the Lahey Clinic 11 and one case from the Mayo Clinic. 12 In all three cases the endocrine disease preceded the neurologic syndrome and coexisted with it for many months. The Guillain-Barré syndrome was preceded by an upper respiratory infection in all cases. The symptoms were severe in all the cases, with marked sensory and motor deficit and pronounced respiratory difficulties. The Cushing's syndrome diagnoses were well documented and pathologically ascertained to be adrenal hyperplasia. This was true of our own case. Two of the cases had some residual postoperative neurologic impairment of many months' duration, during which time they were maintained on cortisone. The third case died of unknown causes three months postoperatively.

The appearance of the Guillain-Barré syndrome in a patient being treated with large doses of cortisone for rheumatoid arthritis has been reported.<sup>13</sup> The patient had been maintained on 100 mg./day for the three years prior to the onset of symptoms. When the neurologic illness developed, the cortisone dosage was increased to 300 mg./day and was subsequently tapered to 100 mg./day, with gradual resolution of the neurologic manifestations.

Another occurrence of the Guillain-Barré syndrome in the face of high doses of exogenous steroids involved the treatment of erythema multiforme with cortisone.<sup>14</sup> The erythema multiforme subsided as the neurologic symptomatology emerged. The patient succumbed to respiratory complications while on cortisone.

A multitude of causative organisms and agents have been implicated in the Guillain-Barré syndrome. <sup>15-25</sup> In recent years the concept of the syndrome as an allergic manifestation has become prevalent. <sup>4, 26-28</sup> An experimental polyneuritis of rabbits, similar in many respects to the Guillain-Barré syndrome, has been produced by the injection of peripheral nervous tissue and adjuvants. <sup>29</sup> This condition appears 14 days after the inoculation and is a noninfectious inflammatory disease of peripheral nerves immunologically induced.

Characterizing pathologic features of the Guillain-Barré syndrome have not been definitively established. The correlation between clinical status and pathologic findings is often tenuous. In some rapidly fatal cases no specific changes have been found. Histologic studies have shown that the pathologic changes of the disease are not those of a primary inflammation.<sup>1, 80</sup> An extensive review of the subject, based on the findings in 50 fatal cases,<sup>1</sup> showed that for the initial three to four days of the illness edema of the nerve roots was the only change. This was followed by degeneration of myelin sheaths and axon cylinders. A cellular reaction developed by the second week of the illness. Some cases of the same duration had minimal or no change.<sup>29</sup>

The frequently reported sequence of a nonspecific insult or infection, followed after a latent period by a polyneuritis, is compatible with an allergic disease. The histologic picture supports this concept. ACTH and cortisone have been used in treatment on this basis.

A number of favorable reports on the use of these drugs have appeared since 1952. The reported cases were frequently preceded by upper respiratory infections and had latent periods ranging from one to five weeks. The patients treated were generally in extremis, with severe sensory and motor involvements and respiratory complications. The reports have been in agreement on several aspects of the therapeutic results. These compounds caused a rapid reversal of the downhill course of the disease. Responses have been observed in 30 minutes 6 and several hours, 4 but were usually seen after several days of therapy. The treatment did not shorten the duration of the disease. After the initial reversal of the downhill course, recovery was gradual and prolonged. The drugs apparently are best used early in the progressive phase of the disease, at a time when nerve root edema has caused a functional but not yet a structural paralysis.8, 30 Good results, however, have been obtained when treatment was instituted one to four weeks after the onset of symptoms. No consistent data on adequate duration of therapy have been obtained. Relapses due to insufficient duration of treatment have been reported.4,7 Complete remissions after five days of therapy and relapse after seven days of therapy have occurred.6,7 The effective doses of cortisone have ranged from 50 mg. per day to 200 to 300 mg, every eight hours. In general, the initial reversal of the downhill course of the polyneuritis was associated with a rise in the cerebrospinal fluid protein. The highest protein levels were found in the early convalescent phase. These fell during the gradual recovery period.8

Some reports on the use of these drugs in the Guillain-Barré syndrome have been unfavorable.<sup>31-83</sup> One series showed a response in only about 50% of cases.<sup>51</sup>

A therapeutic agent proposed for use in the Guillain-Barré syndrome would be difficult to evaluate. Although the syndrome is not rare, it is not common enough for any center to have gathered sufficient numbers of cases for a conclusive study. Great variation in time is to be expected between the onset of the symptoms and the institution of therapy. Evaluation of therapy is made difficult by the nature of the natural history of the syndrome. Experience with the disease has led to a cautious philosophy of prognosis. It is not always true that, once the downhill course of the disease is reversed and recovery begun, it will continue to improve uninterruptedly.<sup>34</sup> A case running a benign course toward recovery may suddenly relapse into a new set of symptoms which threaten life. It is equally true that there are cases of severe paralysis of doubtful recovery that suddenly change to a picture of rapid return of function. These considerations are involved in the acceptance of a therapeutic response to a drug.

One may infer from the variability of the disease course and the multiplicity of etiologic agents that the syndrome is a symptomatic expression of a pathophysiologic process common to several diseases. The protean nature of the literature on the polyneuritis has led to the conclusion that a number of entities are being subsumed under the term, Guillain-Barré syndrome.

## SUMMARY

A case of Cushing's syndrome and Guillain-Barré syndrome is reported. Cortisone therapy in the Guillain-Barré syndrome is discussed.

#### SUMMARIO IN INTERLINGUA

Un feminina de 30 annos de etate notava debilitate, paresthesias, e perdita de sensation in le extremitates inferior. Le liquido cerebrospinal contineva 944 mg% de proteina e nulle cellulas. Iste constatationes esseva de accordo con le diagnose de syndrome de Guillain-Barré. Al tempore del declaration del disordine neurologic, ronditate facial, episodios depressive, augmento del peso corporee, e hypertension appareva. Ben que le stato neurologic se meliorava, le altere symptomas del patiente progredeva, e un complete tableau clinic de syndrome de Cushing se disveloppava. Isto esseva confirmate per le appropriate studios laboratorial. Le patiente respondeva ben a adrenalectomia bilateral.

Reportos favorabile relative al uso de steroides adrenal in le phase acute de syndrome de Guillain-Barré ha apparite in recente tempores. Le disveloppamento de iste morbo in le presentia de alte valores del excretion de endogene steroides adrenal esseva consequentemente inexpectate e inusual.

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## MYXEDEMA COMA\*

# By John J. Kelly, M.D., and Henry H. Sherk, M.D., Philadelphia, Pennsylvania

THREE cases of myxedema with terminal coma were described in 1888 by a committee of the Clinical Society of London.<sup>1</sup> Although similar cases of "myxedema coma" have been reported subsequently,<sup>2, 3</sup> little attention was directed

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specifically toward this complication until 1953, when Le Marquand et al. presented two such patients.<sup>4</sup> Since then, 23 cases have been described.

In view of the rare occurrence of myxedema coma, it was deemed appropriate to report another patient who became profoundly myxedematous over a period of years, lapsed into coma suddenly, and died shortly after admission to the hospital. Necropsy findings are described and the other reported cases of myxedema coma are briefly reviewed.

## CASE REPORT

An 80 year old white woman was admitted to the medical service of the Jefferson Medical College Hospital on March 18, 1957, with the complaint of shortness of breath with substernal and left shoulder pain. In the preceding 15 years she had been a slow-moving, unconcerned person who found it necessary to rest frequently and sleep long hours. She was made very uncomfortable by cold weather, and even during hot summer days would remain in an upstairs room not seeking a cooler place. Her voice was characteristically low-pitched and hoarse. She was chronically constipated and took laxatives almost daily. Her hearing had been lost gradually over the six or seven years preceding her admission.

Five years prior to admission, swelling of both ankles began to occur, usually after the patient had been walking or standing for long periods of time. Her characteristic lassitude became more marked, and she would fall asleep in the midst of her daily activities. She complained of stiffness in her knees, developed a puffy appearance, and her hair became sparse and dry. She was treated by a physician for almost two years for "an anemia." Her condition grew worse, however, and about a year before admission she developed dyspnea and substernal pain on exertion. Digitalis and nitroglycerin were prescribed, with considerable relief of these complaints.

Two weeks prior to admission the patient experienced a severe, crushing pain in her chest, brought on by exertion and relieved by three nitroglycerin tablets. Orthopnea, exertional dyspnea, marked pitting edema of both ankles, and short bouts of substernal pain persisted during the two weeks before admission in spite of treatment with digitoxin, mercurial diuretics and nitroglycerin. On the day of admission she experienced a prolonged episode of substernal pain which radiated to her left shoulder and necessitated hospitalization.

At the time of admission the patient was noted to be a pale, puffy, aged white woman in no immediate distress. She was oriented as to time and place but seemed otherwise confused and vague. The temperature was 96.0° F.; pulse, 60 per minute; blood pressure, 160/80 mm. of Hg; respiration, 20 per minute. The skin was dry and scaling, the hair fine and thin, and the eyebrows were sparse, especially in the outer portions. The tongue and lips were thick, the mouth hung open, and the voice was so slow, hoarse and slurred that one could hardly understand her. The neck was thick and full. No cervical vein distention was noted, and the thyroid gland was not palpable. The submaxillary glands seemed slightly enlarged. Hearing was very poor. Expansion of the chest was impaired bilaterally. Dullness was noted at both bases posteriorly, and diminished breath sounds and crepitant râles were elicited at both bases. The heart was slightly enlarged, and a grade II systolic murmur was heard over the aortic and mitral areas. The remainder of the examination, including the neurologic examination, yielded results within normal limits. The clinical impressions were severe myxedema and arteriosclerotic heart disease with congestive failure.

Laboratory studies obtained on admission revealed a hemoglobin of 9.5 gm.% and a hematocrit of 30.5%. The white cell count was 5,400 per cubic millimeter, with

a normal differential count. The fasting blood sugar, blood urea nitrogen, creatinine, serum proteins and A/G ratio were within normal limits. Liver function studies were also normal. The cholesterol was 326 mg. per 100 ml., and the cholesterol esters were 263 mg. per 100 ml. The carbon dioxide combining power was 27.3 mEq./L.; chlorides were 84.0 mEq.; sodium, 115 mEq.; potassium, 3.9 mEq. The VDRL and Kolmer test for syphilis were negative. The urinary excretion of 17-ketosteroids was 2.2 mg. per 24 hours, and the protein-bound iodine was 0.9  $\mu \rm g$ . per 100 ml

The patient's condition remained unchanged during the first two days of her admission. She was treated during this time with Gitalin, Peritrate, Choledyl, nitroglycerin and aminophylline in appropriate dosages. On the third day of admission, while being catheterized, she suddenly lapsed into an unconscious state from which she could not be roused even with painful stimuli. Very shortly thereafter the report of the protein-bound iodine 5 was received (0.9 µg.%). The diagnosis of myxedema was confirmed, and myxedema coma was strongly suspected. Therapy was begun with 25 µg. of tri-iodothyronine every four hours via a stomach tube. Twenty-five milligrams of Solu-Cortef were given intravenously immediately, and 50 mg, were placed in an intravenous infusion of 500 ml, of physiologic saline. The patient was covered with several blankets and placed in an oxygen tent. Although these measures were continued, she remained in coma and her body temperature did not rise above 96.5° F. Her abdomen became quite distended. A rectal tube was inserted, with very little relief. Neurologic examination revealed a delayed patellar reflex bilaterally, but the rest of the physical examination was the same as that described on admission.

On the morning of the fourth day of admission, the respirations had fallen to six per minute. In a short time they ceased entirely and a pulse could not be obtained. Intracardiac epinephrine was administered, to no avail, and the patient was pronounced dead at 8:30 a.m., March 22, 1957. A total dose of 250  $\mu g$ . of triiodothyronine, 150 mg. of Solu-Cortef and 125 mg. of cortisone had been given during the 40 hours that she had been in coma.

Necropsy Findings: The thyroid was small and fibrous, weighing 10 gm., and the scattered islands of thyroid follicles present represented about 15% of the total gland weight. The pituitary was normal in size and contained scattered eosinophilic pseudopregnancy cells. The adrenals were normal in size, and there was diffuse vacuolation of cells of the cortex. Sections of the skin revealed atrophy of the rete pegs and, on staining with toluidine blue, a thin layer of mucopolysaccharide was demonstrated just beneath the epidermis. The skeletal muscle was markedly edematous, with separation of the muscle fibers and loss of striation. The tongue was markedly enlarged and thick. Sections for microscopic study disclosed edema, separation of the muscle fibers and mucoid degeneration. The heart weighed 540 gm. There was evidence of left ventricular hypertrophy and severe calcification of the aortic and mitral valves, along with calcification and narrowing of the coronary ostia. The muscle bundles of the heart were swollen and separated; there were areas of mucoid degeneration of the cardiac fibers. Sections of the aorta and pulmonary vessels revealed mucoid degeneration of the muscularis, with generalized severe arteriosclerosis of the entire vascular tree. The lungs were congested and edematous, with atelectasis of the lower lobes bilaterally. There were 1,500 c.c. of clear fluid in each pleural space. Minimal arteriosclerosis and arteriolosclerosis were seen in the kidneys.

The brain weighed 1,110 gm. Arteriosclerosis of the cerebral and basilar arteries was present, but there was no evidence of thrombosis or infarction. Extensive review of the microscopic sections of all portions of the brain revealed only diffuse degenerative changes compatible with an advanced degree of cerebral arteriosclerosis.

## DISCUSSION

The series of events described in the report, coupled with the clinical, laboratory and autopsy findings, coincides closely with previous cases of myxedema coma described in the French, British and American literature.<sup>4, 6-18</sup> In addition, we have found several other cases where the clinical picture and mode of exitus strongly suggest the presence of myxedema coma, although it was not so recognized.<sup>10-21</sup>

Myxedema coma occurs most frequently in females, only three of the 23 cases having been reported in males.8-cases 1, 3, 4 It has been described in patients 36 15 and 84 6 years of age, but is most common in the seventh decade, 17 of the 23 cases falling between 59 and 70 years of age. 4-case 1; 7, 8, 11-14, 16-18 The duration of myxedema before the onset of coma is reported as from two weeks 4-case 1 to 20 years; 9 the mean duration is 4.7 years. The onset of coma in some cases was gradual; in others, sudden onset was precipitated by infection, heart failure, or some other major stress. All of the cases reported have been typically myxedematous clinically and, in some, marked hypothermia, with body temperatures of 74° to 83°, has been described. 8-cases 1, 2; 12-cases 2, 4; 14, 16, 17 In the patient herein reported, however, the temperatures recorded may not clearly reflect the degree of hypothermia present, since they were taken rectally with a clinical thermometer which did not record temperatures below 96°. Of interest also is the observation that the electrocardiogram did not show the small ORS complexes and flattened T-waves characteristic of the myxedema heart,28,24 but rather showed the changes of left ventricular hypertrophy and myocardial damage.

Therapeutic measures employed have included thyroid preparations in widely varying amounts, steroids, amphetamine, intravenous fluids, rewarming, and oxygen. Results have been poor, with only five reported survivals of myxedema coma. 6, 7—case 1; 12—case 3;15 Autopsy has uniformly revealed the absence, atrophy or fibrosis of the thyroid gland. Considerable attention has been given to the changes that occur in the brain with advanced cerebral arteriosclerosis, edema and cerebral atrophy having been described. 9, 11, 15 From the pathologic findings and clinical course in this and other cases, it appears that the onset of myxedema coma may indeed represent severe and in most cases irreversible change in the brain substance, specifically the hypothalamus. The comatose state may be the result of prolonged and profound changes in brain metabolism, due primarily to the myxedema. It is possibly enhanced to a great extent by the progression of severe arteriosclerosis, with decrease in vessel size and consequent diminution in cerebral blood flow. The arteriosclerosis in turn perhaps is accelerated by prolonged elevation in blood cholesterol and lipid levels.<sup>25</sup> With the disruption of hypothalamic function, the thermoregulatory mechanism is deranged and hypothermia and coma develop.

Therapy in this patient consisted of large doses of tri-iodothyronine and hydrocortisone, with general supportive measures of intravenous fluids, oxygen, and warming with blankets. These measures failed to produce any clinical improvement and were undertaken with the knowledge that they might further embarrass the patient's already impaired cardiovascular system. Indeed, the fluids, electrolytes and steroids given may have contributed to the formation of the bilateral pleural effusion found at postmortem examination.

In the future, perhaps the use by the intravenous route of tri-iodothyronine

might be considered in an effort to halt or reverse the myxedematous process. Certainly, more cautious therapy has given poor results.

## SUMMARY

The development of coma is reported in an 80 year old woman with untreated myxedema, probably of 15 years' duration.

The clinical course, therapy and necropsy findings are reviewed and a brief survey of the literature is included.

The probable etiologic factors producing this picture are discussed.

The number of cases cited in the literature, both recognized and suggestive of myxedema coma, indicate this is not so rare an entity as is supposed. The prognosis is generally poor. Use of intravenous, rapid-acting thyroid preparations may be a therapeutic tool of worth and merits further trial.

#### ACKNOWLEDGMENT

The authors gratefully acknowledge the help and advice of Dr. Joseph J. Rupp in the study of this case.

#### SUMMARIO IN INTERLINGUA

Es reportate le disveloppamento de coma in un femina de 80 annos de etate, con myxedema non tractate de un duration de probabilemente dece-cinque annos.

Le patiente esseva admittite al Hospital del Collegio Medical Jefferson con le gravamines de dyspnea e dolores substernal e sinistro-humeral. Illa reportava un historia de 15 annos de intolerantia pro frigido, preferentia de temperaturas inusualmente calide, constipation chronic, perdita gradual del audito, e le disveloppamento de raucitate gravisonante. Cinque annos ante su hospitalisation, illa habeva notate tumescentia del cavilias, grados plus marcate de su lassitude, e le disveloppamento de un complexion inflate con sparsitate e siccitate del capillos. Durante approximativemente duo annos illa esseva tractate pro "anemia." Su condition se pejorava, e durante le anno precedente su hospitalisation, illa disveloppava dyspnea e angina post effortio. Su hospitalisation esseva precipitate per accessos de dolores thoracic e le disveloppamento de signos de disfallimento cardiac.

Al tempore de su admission al hospital, le patiente monstrava le aspectos characteristic de grados sever de myxedema e, in plus, de morbo cardiovascular arterio-

sclerotic con disfallimento congestive.

Studios laboratorial monstrava 9,5 g de hemoglobina e un hematocrite de 30,5. Le sucro del sanguine in stato jejun, le nitrogeno de urea del sanguine, le nivello de creatinina, le proteinas del sero, e le proportion de albumina a globulina esseva intra limites normal. Studios del function hepatic monstrava nulle anormalitate Le concentration de cholesterol esseva 326 mg per 100 ml; illo del esteres de cholesterol 263 mg per 100 ml. Le excretion urinari de 17-cetosteroides esseva 2,2 mg in 24 horas, e le iodo ligate a proteina amontava a 0,9 µg per 100 ml.

Le tertie die de su sojorno al hospital le patiente cadeva a in un stato de inconscietate. A iste tempore le reporto relative al iodo ligate a proteina esseva recipite. Le diagnose de myxedema esseva confirmate, e le suspicion de coma per myxedema esseva forte. Le plus vigorose therapia possibile esseva initiate immediatemente, sed le matino del tertie die al hospital, le frequentia del respiration habeva descendite a sex per minuta. Postea le respiration cessava. In le curso del tractamento, un dose total de 250 µg de tri-iodothyronina, de 150 mg de Solu-Cortef, e de 125 mg de cortisona esseva administrate in un periodo de 40 horas.

Al necropsia, le corpore thyroide esseva micre e fibrose, e le disperse insulas de folliculos thyroide representava 15 pro cento del peso del corpore. Le glandula pituitari esseva normal in su dimensiones e contineva disperse cellulas eosinophilic de pseudopregnantia. Le adrenales esseva normal in dimension. Esseva notate vacuolisation diffuse de cellulas del cortice. Sectiones cutanee, tincturate blau con toluidina, revelava un strato tenue de mucopolysaccharido. Sectiones muscular monstrava edema, degeneration mucoide, e perdita de striation. Le corde e le arbore vascular exhibiva signos de arteriosclerosis sever. Le cerebro pesava 1.100 g. Arteriosclerosis del vasos cerebral esseva notate, sed nulle signo de thrombosis o infarcimento esseva evidente.

Le caso hic describite coincide frappantemente con alteres trovate in le litteratura francese, britannic, e american. Coma per myxedema occurre le plus frequentemente in femininas durante le septime decennio del vita. Le declaration pote esser gradual o subite e producite per un stress major. Omne le casos esseva clinicamente myxedematose, e in plures marcate grados de hypothermia esseva reportate.

Le mesuras therapeutic usate ha includite preparatos thyroide, steroides, amphetamina, calor, e oxygeno.

Studios pathologic e etiam le curso clinic mesme pare indicar que coma in myxedema representa sever alterationes de character irreversibile in le substantia del cerebro, specificamente del hypothalamo, resultante—possibilemente—de profunde alterationes in le metabolismo cerebral que esserea le effecto del myxedema e que esserea promovite per le reduction del fluxo de sanguine cerebral que es le effecto del accompaniante arteriosclerosis.

In le futuro, on poterea prender in consideration le uso de tri-iodothyronina per via intravenose in le effortio de arrestar o reverter le processo myxedematose.

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# ROENTGENOLOGIC AND CLINICAL ASPECTS OF MULTIPLE MYELOMA WITH REPORT OF AN UNUSUAL CASE \*

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MULTIPLE myeloma was first described as an entity in 1889 by Kahler, who stated that the following features are characteristic of this disease:

- 1. Bone pain and abnormal fragility.
- 2. Anemia, weakness and loss of weight.
- 3. Presence of Bence Jones proteins in the urine.

The original description of multiple myeloma refers to diffusely infiltrating, intramedullary, multiple tumors which consist of myeloma cells. These cells could best be described as plasmoid cells, since they have the characteristics of young plasma cells. The tumors, frequently referred to as plasmacytomas, are found mainly in the flat bones.

Today, we know that multiple myeloma may also start as a solitary myeloma, limited to a single bone for many years, and eventually spread to other portions of the skeleton.

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In addition, an extramedullary type of multiple myeloma has been described which originates in the soft tissues, but in the terminal stage produces intramedullary infiltrations also, indistinguishable from the more common type of multiple myeloma. In the advanced stages an extra-osseous spread occurs into various organs, such as the liver, lymph nodes, lungs, kidneys, uterus, ovaries, adrenals and pancreas.

Clinically, multiple myeloma is characterized by fatigue and anemia, and often by bone pains, mainly in the back and thorax. These pains are more frequently found in the early stages and, as a rule, less commonly in the more advanced stages. Occasionally, a spontaneous fracture may be seen as a first sign. The condition is extremely rare in children and young adults, and develops in patients over 40 years of age. There is a slight male predominance.

Since the typical myeloma cells infiltrate the red bone marrow, the sternum is invariably affected, and a definite diagnosis can be established by means of a sternal puncture. Blood chemistry may sometimes reveal a marked hypercalcemia, which indicates only a rapid decalcification. This is not specific for multiple myeloma. There is also an increase in the serum proteins, particularly the globulin.

## ROENTGENOLOGIC CLASSIFICATION

The roentgenologic appearance of the bone lesions is supposedly characteristic of multiple myeloma. Most textbooks still describe the multiple and sharply defined "punched-out" areas of rarefaction, which are disseminated but clearly isolated from one another, as the typical lesions of multiple myeloma. In recent years, however, this concept has been discarded. Camp, in his discussion of Kinney's 1 paper, states that there is no characteristic roentgenologic picture which will permit an unquestioned diagnosis of multiple myeloma, and Lichtenstein and Jaffe 2 claim that the discrete, well defined destructive lesions are rather exceptional.

Recently, Heiser and Schwartzman <sup>3</sup> published a paper in which an attempt is made to classify the bone changes of multiple myeloma according to their

various radiologic manifestations. They distinguish six groups:

1. Normal appearance of the bones.

2. Osteoporosis.

3. Osteoporosis and osteolysis.

4. Sharply circumscribed bone destruction.5. Poorly circumscribed bone destruction.

5. Toolly circumscribed bone destruc

6. Severe bone destruction.

Personally, we feel that this classification does not really distinguish various types of the disease but rather various stages of advancement, which may vary even within the same individual.

In our opinion the radiologic changes in multiple myeloma are the result of several factors, each contributing to the appearance of the lesion. We believe that the rate of progression, the reactive forces of the surrounding tissues (as an attempt at repair) and the subsequent secondary changes are responsible for the multiform radiologic appearance. Thus, the various manifestations of multiple myeloma can be explained as follows:

1. Early stages without bone destruction. If no bone pains are present and the infiltration of the red bone marrow is not advanced, no roentgenologic osseous changes are found.

2. Multiple myeloma simulating simple osteoporosis. There is no actual bone destruction, but marked demineralization. The osteoporosis may be caused by disuse due to severe pain. Another reason is the nutritional dis-

turbance produced by a partial blocking of blood supply.

3. Bone destruction without attempts at repair. This group is characterized by "punched-out" lesions, and represents only a phase in the course of the pathologic progression. The lesions are sharply defined and the margins show no bone condensation whatever. This manifestation, although most characteristic of multiple myeloma, is actually an uncommon finding, and it changes as soon as the lesions grow and become confluent. At this stage they resemble osteolytic metastases.

4. Multiple myeloma simulating osseous metastasis of a mixed type (partial osteolytic, partial osteoplastic). This appearance can be explained by a slight attempt at repair, resulting in irregularity of the lesion, and by some

mottling due to recalcification.

5. Multiple myeloma simulating giant cell tumor, fibrous dysplasia, hyperparathyroidism or hydatid cysts. This peculiar manifestation is most apt to be seen in myeloma of a slow progression, where "walling off" reactions of the unaffected bone may enter into the picture. This form is usually seen in the relatively benign solitary myeloma, which is characterized by its slow growth over a period of many years. However, most of these cases terminate as typical multiple myelomas.

6. Multiple myeloma with a predominant feature of pathologic fractures. This manifestation should not be considered as a special group, since pathologic fractures may occur subsequent to marked osteoporosis as well as to extensive

bone destruction.

The fact should be emphasized that the given classification describes manifestations or pattern only, and not groups or types, since several radiologic appearances can be present in the same individual at the same time. This radiologic multiformity of multiple myeloma is illustrated by the case here presented, which in addition demonstrates clinical aspects differing greatly from the typical picture of this disease.

## CASE REPORT

History: The patient was a 24 year old Negro woman with complaints of inability to walk and pain in the lumbar region and right hip. In September, 1955, patient had awakened in the morning, sneezed and felt a sharp pain in the sacral region. The pain was not constant, and was aggravated by moving, change of position, sneezing, coughing and laughing. The pain radiated to the right hip occasionally. When recumbent, the patient preferred the prone position. She reported that after an x-ray examination by a general practitioner a diagnosis of a "misplaced right hip" had been made.

The patient had had bronchial asthma from the age of 16 to 19—a few severe attacks, but had never been hospitalized. There was no history of fracture or trauma.

The patient did not remember any other disease.

TABLE 1
Blood Chemical Tests

Date	Glucose	B.U.N.	Tot. Prot.	Alb.	Glob.	Ca	Alk. Phosph.	Acid Phosph.	P	Chole
10/10	81	13.4	7.7	4.3	3.4	10.6	4.2	-	4.3	
10/17	83	12.3	7.8	4.5	3.3	10.8	3.9	0.34	4.0	215
10/27	88	12.1	7.1	4.5	2.6	11.0	3.4	0.41	3.8	
11/3	84	11.7	7.6	4.3	3.3	10.2	3.5	-	4.0	235
11/29	89	13.0	7.1	4.0	3.1	11.0	4.1	1:	3.6	-
3/9	82	11.0	7.2	4.5	2.7	10.8	3.3	-	3.8	1 -
3/18	91	12.5	6.8	5.0	1.8	10.9	3.7	0.12	3.7	225
3/23	86	11.6	8.0	4.7	3.3	10.7	3.0	0.48	4.2	230
4/2	89	12.0	7.1	4.5	2.6	11.4	3.2		4.4	-
4/6	86	11.0	7.2	5.2	2.0	9.9	3.9		4.1	-
8/8	87	11.5	7.2	4.5	2.7	10.7	4.3	-	3.9	221
Average	86	12.0	7.3	4.5	2.8	10.7	3.7	_	4.0	225

The patient's mother was alive and suffered from occasional dizziness. Her father had died of unknown causes. The patient had two brothers and two sisters who were well.

The patient was unmarried, had had no children. She denied smoking, drinking or drug addiction. Menarche had occurred at the age of 12. She suffered from

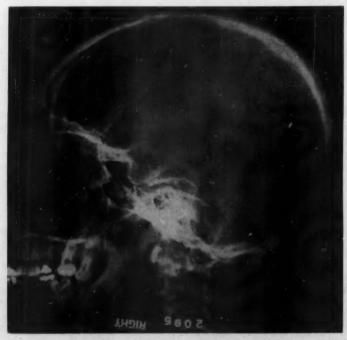


Fig. 1. Several small, round, punched-out areas of rarefaction are noted in the frontal and parietal bones.

premenstrual cramps; the menses were regular, with a 24 day interval and lasting for four days.

Clinical Findings: The patient was well developed and well nourished. She complained of pain in her back, but was not in acute distress. Pulse, 100 and regular; blood pressure, 120/78 mm. of Hg.; respiration, 18; temperature, 99.2° F.

The skin revealed no abnormal findings. The head showed a normal contour, without palpable masses or tenderness.

The eyes showed slight pallor of the sclerae but no icterus. Pupils were round, regular and equal, and reacted to light and accommodation normally. Extraocular movements were normal. Ears, nose and throat revealed no abnormal findings. The teeth were in poor condition.

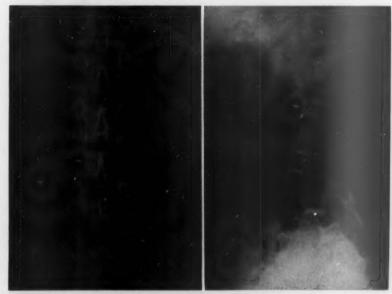


Fig. 2. There is a compression fracture of the second lumbar vertebra, with collapse and anterior wedging of the vertebral body.

The neck was supple, the trachea in the midline, and the thyroid not palpable. No evidence of lymphadenopathy was found. The breasts were equal in size, and there was no mass or tenderness.

On examination of the heart, the point of maximal intensity was in the fifth intercostal space; there was no sign of enlargement on percussion, and no thrills or murmurs were heard. There was regular sinus rhythm. Ventricular rate and pulse rate were both 100. The pulmonic second tone was not accentuated.

The lungs were clear on percussion and auscultation.

The abdomen was flat and soft, and without palpable masses, tenderness or rigidity. The liver, spleen and kidneys were not palpable. The peristaltic sounds were normal.

The back showed no tenderness in the costovertebral angles or over the vertebrae. The genitalia revealed normal pubic hair and normal adult female development. There were no hemorrhoids. The stool was normal in color.

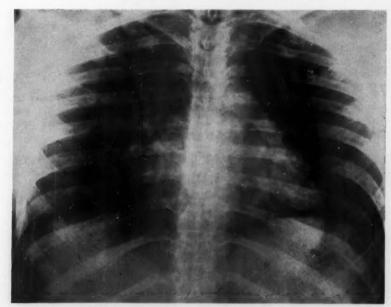


Fig. 3. The ribs show multiple, round, punched-out areas of rarefaction.



Fig. 4. The pelvis and the upper femora show several round areas of rarefaction.

Both upper extremities and their reflexes were normal. The knee and ankle jerks were very hypoactive on both sides. There were no pathologic reflexes, spasticity or rigidity. The strength in all extremities was both equal and normal. The patient had pain only in the upper lumbar region.

Laboratory Findings: The blood count showed a slight anemia (3.5 to 4.3 million red blood cells), with a hemoglobin of 10.5 to 13.8 gm.; white blood cell count on various examinations varied from 2,500 to 11,000; the differential count was within normal range. Sedimentation rate was moderately increased (25 to 40). Reticulocytes amounted to 4%. (These values are average figures from 11 examinations within 10 months.)

Blood chemical tests revealed no abnormal findings (table 1). (The following values represent the average figures obtained from 11 examinations within 10 months;



Fig. 5. Note rapid progression in number and size of myelomatous lesions five months later.

glucose, 86 mg.%; blood urea nitrogen, 12 mg.%; albumin, 4.5 gm.%; globulin, 2.8 gm.; calcium, 10.7 mg.%; phosphorus, 4.0 mg.%; alkaline phosphatase, 3.7 S.J.R. units; cholesterol, 225 mg.%.)

The urine showed normal values and on seven occasions no Bence Jones proteins were found.

Roentgen Findings: X-ray examination of the skull revealed several small, round areas of rarefaction without bone reaction at their margins (figure 1).

X-ray examination of the bony thorax and the lumbar spine showed demineralization of the bones, with thinning of the cortex, characteristic of osteoporosis. In addition, the body of the second lumbar vertebra appeared to be destroyed, resulting in a marked compression fracture (figures 2, 3). Roentgenologically, the pelvic bones and upper femora showed numerous sharply defined, round, "punched-out" areas of rarefaction. These changes markedly increased in size and number during the last five months of observation (figures 4, 5).

Because of these outstanding x-ray findings a diagnosis of multiple myeloma was strongly suspected.

Bone Marrow: Three bone marrow studies confirmed the diagnosis of multiple myeloma. There was a striking increase in plasma cells (80%). Some of them were normal, while others contained vacuoles or were large with multiple nuclei. There was no rouleaux formation (figure 6).

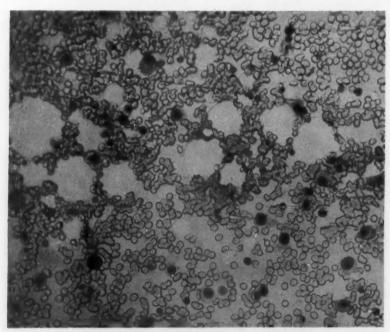


Fig. 6. Bone marrow from sternal puncture shows increase in plasma cells, some containing vacuoles or multiple nuclei characteristic of myeloma.

A bone biopsy from the left iliac crest was reported as normal.

Electrophoresis: There were no specific findings.

Clinical Course: Patient remained afebrile. Because of the diffuse spread of the lesions, no effective treatment was available. The patient was treated with cortisone, urethane, testosterone, depo-ACTH, hematinic liver and Meticorten. She was given 500 c.c. of whole blood, and for a short period of time received x-ray therapy. Aspirin, codeine and Demerol were given intermittently for analgesia.

At present the patient is semi-ambulant. She is nervous and rather irritable,

but seldom complains of pain.

## COMMENTS

The case presented above shows a peculiar discrepancy with respect to its clinical symptoms, laboratory findings and roentgenologic changes. Because

of the almost complete lack of corroborating clinical findings, the diagnosis of multiple myeloma would not have been suspected. In view of the unusual combination of clinical and laboratory findings, and in spite of the most characteristic roentgenologic appearance, the diagnosis of multiple myeloma still seemed to be questionable, but was finally confirmed by bone marrow studies.

The following demonstrates in particular the atypical symptomatology of this case when contrasted with the usual reported findings:

1. Unusual age: This case is very unusual because of the age—24 years. The medical literature reveals some atypical cases, but multiple myeloma usually occurs in middle aged people (see tables 2 and 3).

TABLE 2
Age of Incidence of Multiple Myeloma

	Number of Cases	Age	Younges Age (years)
Adams et al.4	61	89% of cases over 50 years	31
Snapper et al.5	97	95% of cases over 40 years	29
Wintrobe <sup>6</sup>		80% of cases over 40 years	
Meacham <sup>8</sup>	51	82.3% of cases over 50 years	35
Brichtenbucher and Hertzog®	95 35	78% of cases over 50 years	31
Lichtenstein and Jaffe <sup>2</sup>	35	75% of cases over 40 years	
Kesterson and McSwain <sup>10</sup>	14	86% of cases over 44 years	29
Geschickter and Copeland <sup>11</sup>	425	80% of cases over 40 years	32

TABLE 3
Atypical Cases of Early Onset

	Number of Cases	Youngest Age (years)
Ghormley et al.13	127	4
Slavens <sup>14</sup>	1	4
Rubinstein <sup>15</sup>	1	15
Aegertu and Robbins <sup>18</sup>	13	16 and 32
Wood et al.17	. 1	19
Bayrd and Heck18	83	37
Limarzi <sup>10</sup>	75	40

- 2. Relatively little pain: As we mentioned before, these patients usually suffer from sharp pain in the early stage of the disease, but in this case the patient had widespread lesions before pain occurred. She required analgesia at first, but as the pain became less frequent and less severe her need for it diminished.
- 3. No severe anemia: Because of these widely diffuse lesions a severe anemia might have been expected, but laboratory reports showed only a moderate anemia.
- 4. No Bence Jones protein: Approximately 50% of patients with multiple myeloma have Bence Jones protein in the urine (table 4). In spite of widely disseminated lesions, this patient had negative Bence Jones protein on seven different occasions.
- 5. No hypercalcemia: As shown by the x-rays, the patient had rapidly growing lesions but never had the hypercalcemia which could have been expected.

TABLE 4

Incidence of Bence Iones Protein and Hyperglobulinemia in Multiple Myeloma

	Bence Jones Protein	Hyperglobulinemia %
Adams et al.4	47	52
Snapper et al.6	50	60
Wintrobe <sup>7</sup>	47-65	50
Meacham <sup>8</sup>	33.3	61.2
Brichtenbucher and Hertzog <sup>®</sup>	42	64
Lichtenstein and Jaffe <sup>3</sup>	38	. 50
Bayrd and Heck18	53	73
Limarzi <sup>10</sup>	65	
Atkinson <sup>20</sup>	87	
Magnus-Levy <sup>21</sup>	73	
Geschickter and Copeland <sup>11, 12</sup>	65	
Butts <sup>23</sup>	50	
Gutman <sup>33</sup>	45	
Ghormley et al.18	50	50

6. No increase in globulin: The incidence of increased globulin in multiple myeloma is similar to that of Bence Jones protein (table 4), but laboratory reports in this case showed no increase in globulin.

In contrast to these "negative" findings, the x-ray appearance was very characteristic, revealing (1) punched-out, round areas of rarefaction without bone repair, widely disseminated through the skeleton in "textbook" fashion; (2) osteoporosis of the spine, and (3) compression fracture of the second lumbar vertebra.

## SUMMARY

1. We have attempted to explain the reasons for the multiformity in the roentgenologic appearance of multiple myeloma.

2. We have pointed out that roentgenologic classification of multiple myeloma into various types is not possible. However, various roentgenologic "patterns" may be distinguished which may express the stage of the disease, the rate of progression, and the degree to which reactive forces work at an attempt to repair the damage.

3. We have presented a case of multiple myeloma for its unusual clinical picture and for its very uncommon occurrence in a female patient of 24 years. In spite of the advanced stage—which is documented by a most typical roent-genologic appearance and by pathognomonic bone marrow findings—other characteristic accompanying signs, such as anemia, hyperglobulinemia, hypercalcemia and Bence Jones protein, were missing.

## SUMMARIO IN INTERLINGUA

Le alterationes radiologic de myeloma multiple es le resultato de plure factores que contribue individualmente al apparentia del lesion. Le autores opina que le celeritate del progression, le intensitate del fortias reactive in le histos circumjacente (in le effortio de effectuar un reparo del lesion), e subsequente alterationes secundari es responsabile pro le multiforme configuration radiologic que characterisa iste condition. Assi le varie manifestationes de myeloma multiple pote esser explicate sequentemente:

1. Phases precoce sin destruction de osso. Cellulas tumoric es trovate solmente in le medulla ossee, e nulle alterationes roentgenologic es observabile.

2. Myeloma multiple simulante osteoporosis simple. Le osteoporosis pote esser causate per disturbationes nutritional in consequentia de un bloco partial del provision de sanguine. Non-uso, in consequentia del sever grados de dolor, es possibilemente un causa additional pro le disveloppamento de osteoporosis.

3. Destruction de osso sin tendentia reparatori. Iste gruppo es characterisate per le apparentia punceate, clarmente definite, e ronde del lesiones que monstra nulle condensation ossee a lor margines. Ben que iste forma del lesiones es le plus characteristic de myeloma multiple, illo non es incontrate communmente.

4. Myeloma multiple simulante metastase ossee de typo mixte. Es notate un leve effortio a effectuar le reparo del lesiones que monstra alora un conformation irregular con marmoration que reflecte le processo recalcificatori.

5. Myeloma multiple simulante tumores a cellulas gigante, dysplasia fibrose, hyperparathyroidismo, e cystes hydatidic. Iste configuration es causate per le processo del "immuration" e se incontra plus frequentemente in myeloma solitari de character relativemente benigne.

6. Myeloma multiple con le aspecto predominante de fracturas pathologic.

Iste classification describe manifestationes o configurationes e non gruppos o typos, proque plures del descriptiones pote corresponder al mesme individuo a un sol momento specific.

Myeloma multiple es non solmente capace de exhibir iste multiformitate radiologic. In plus, illo tende a exhibir atypia de su aspectos clinic, como es illustrate per le caso citate in le presente reporto. Le sequente punctos va demonstrar le symptomatologia atypic de iste caso quando illos es comparate con le existente datos statistic.

1. Etate inusual del patiente. Le patiente habeva 24 annos de etate. Le litteratura mentiona solmente sex altere casos de myeloma multiple occurrente a iste o un plus basse etate.

In despecto del extense lesiones ossee, le patiente non se plangeva de grados sever de dolor.

Le anemia non esseva sever. Le numeration erythrocytic medie esseva
 800,000.

4. Proteinas de Bence Jones esseva absente in septe differente examines.

5. Nulle hypercalciemia esseva notate.

6. Le globulina monstrava nulle augmento.

Per contrasto con iste constatationes "negative", le radiographias monstrava multiple areas punceate e ronde de rarefaction que esseva extensemente disseminate a transverso le skeleto, osteoporosis del columna spinal, e fractura de compression in le secunde vertebra lumbar. Le diagnose de myeloma multiple esseva confirmate per constatationes characteristic in le medulla ossee.

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## **EDITORIAL**

CYSTIC FIBROSIS OF THE PANCREAS IN YOUNG ADULTS\*

## I. INTRODUCTION

Cystic fibrosis has only recently become a concern of adult medicine. It is a disease with a short history, introduced to clinical pediatrics in 1938, when three series of necropsied cases were reported independently by Andersen,1 Harper 2 and Blackfan and May.8 At that time three fourths of the patients died before the age of one year, and only rarely did a child with the disease survive to school age. Clinical recognition became progressively more frequent, and at present few cases presenting at pediatric centers escape diagnosis. Until the end of World War II therapy by diet and sulfonamides improved the prognosis of a few cases. With the advent of effective antibiotic agents, however, the life-span of a large proportion of patients was greatly prolonged. Increasing numbers of adolescents and young adults with the disease now present a problem for the practitioners of adult medicine. As experience with these older patients has accumulated, it has become possible to recognize the disease in a few individuals with chronic bronchitis and sinusitis who have survived without benefit of diagnosis or therapy. The older group of patients consists in part of these possibly milder cases and in part of those who were diagnosed in early life before irreparable damage had been done and who responded to therapy.

## II. PRESENT CONCEPTS OF THE DISEASE

Cystic fibrosis of the pancreas is a generalized, hereditary disease, seen in children, adolescents and young adults, in which there is a dysfunction of exocrine glands. In the fully manifested syndrome there is chronic pulmonary disease, pancreatic deficiency, abnormally high concentration of electrolytes in the sweat, and at times, cirrhosis of the liver. It is now recognized, however, that a gradation in or absence of involvement of certain organs or glandular systems usually affected in this disorder is found in some patients and leads to many variations in the clinical picture.

No histologic changes are found in exocrine glands which do not secrete mucus, such as the eccrine sweat, parotid and lacrimal glands. The chemical composition of their secretions, however, is markedly abnormal.

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<sup>1</sup> Andersen, D. H.: Cystic fibrosis of the pancreas and its relation to celiac disease, Am. J. Dis. Child. 55: 344, 1938.

<sup>2</sup> Harner, M.: Congenital statements due to pancreate defeat. Appl. Dis. Childhood.

<sup>&</sup>lt;sup>2</sup> Harper, M.: Congenital steatorrhea due to pancreatic defect, Arch. Dis. Childhood 13: 45, 1938.

<sup>&</sup>lt;sup>3</sup> Blackfan, K., and May, C. D.: Inspissation of secretion, dilatation of the ducts and acini, atrophy and fibrosis of the pancreas in infants, J. Pediat. 13: 627, 1938.

The basic pathologic change in mucus-producing glands consists of an accumulation of abnormal secretions leading to dilatation of the secretory gland itself. This lesion may be found throughout the body, but it gives rise to symptoms only when organs such as the pancreas and liver are involved. The most striking pathologic changes are in the pancreas, in which there is obstruction of the large and small ducts with amorphous eosinophilic concretions, with consequent dilatation of acini and degeneration of parenchyma, which eventually becomes replaced by fibrous tissue The islands of Langerhans are generally intact. Obstruction of bile canaliculi by similar material leads to foci of biliary cirrhosis. At times the hepatic lesions are more extensive, giving rise to a distinctive type of multilobular biliary cirrhosis.

The incidence of cystic fibrosis is estimated as being in the order of 1 in 1,000 live births. Cystic fibrosis has striking racial predilections, and while found equally in all branches of the white race, it is uncommon in

Negroes and has never been described in Mongolians.

The basic defect in cystic fibrosis is not known as yet, although a common factor must be postulated to explain the malfunction of so many exocrine glands so different in the products they elaborate. Whatever the nature of the basic defect, it is genetically determined, and most of the studies 4, 5, 6 have concluded that it is transmitted as a recessive character. There is some uncertainty as to whether a single gene in the homozygotic condition can account for all of the manifestations of the fully expressed clinical picture, or whether an interaction of several genes or environmental factors may affect genic expression.4 Increasing evidence suggests that the heterozygous state may give rise to some manifestations, and the gene may be more widespread than previously appreciated.7

The symptomatology of cystic fibrosis has been reviewed in several recent publications.8,9,10 It will be sufficient to mention here that chronic pulmonary involvement usually dominates the clinical picture and determines the fate of the patients. Because of the difficulty in removing the abnormal bronchial content there is widespread and at times severe bronchial obstruction leading to chronic emphysema, to secondary bronchopneumonia and at times to death. If the infection is controlled with the aid of antibiotic agents, on the occasion of another intercurrent respiratory or other infection

Heinemann, London, p. 50.

<sup>7</sup> di Sant'Agnese, P. A.: Recent observations on pathogenesis of cystic fibrosis of the

pancreas, Pediatrics, in press.

8 Shwachman, H., Leubner, H., and Catzel, P.: Mucoviscidosis, Advances Ped. 7: 249,

<sup>9</sup> di Sant'Agnese, P. A.: Cystic fibrosis of the pancreas, Am. J. Med. 21: 406, 1956. 10 Andersen, D. H.: Cystic fibrosis of the pancreas, J. Chronic Dis. 7: 58, 1958.

<sup>&</sup>lt;sup>4</sup> Andersen, D. H., and Hodges, R. G.: Celiac syndrome. V. Genetics of cystic fibrosis of the pancreas with a consideration of etiology, Am. J. Dis. Child. 72: 62, 1946.

<sup>5</sup> Goodman, H. O., and Reed, S. C.: Heredity of fibrosis of the pancreas: possible mutation rate of the gene, Am. J. Human Genet. 4: 59, 1952.

<sup>6</sup> Carter, C. O., in Bodian, M.: Fibrocystic disease of the pancreas, 1952, William

the sequence can repeat itself. Any one of these attacks may be fatal. At some time in the course of their disease, pulmonary involvement is present in virtually all patients.

In the great majority of patients with fibrocystic disease pancreatic deficiency is found. Indeed the pathologic changes in the pancreas and the clinical effects of pancreatic deficiency first attracted the attention of investigators and gave the disease its name. Absence of trypsin, lipase and amylase leads to impaired digestion and absorption of foodstuffs. The stools are large, foul and unformed, there is steatorrhea and azotorrhea. Liposoluble vitamins are lost through the feces. The appetite is frequently ravenous and malnutrition may occur despite an apparently adequate dietary

intake.

In over 99 per cent of patients with cystic fibrosis chloride and sodium levels in the sweat are markedly increased. In such patients the sweat glands are unable to conserve salt, although the renal and adrenal cortical function is normal.<sup>11</sup> Massive loss of sodium chloride in the sweat may lead to serious and at times fatal complications in hot weather and occasionally in other circumstances. To date this electrolyte abnormality of sweat has not been found in any other disease, with the exception of untreated adrenal insufficiency, and is therefore of great diagnostic assistance.

Among the less usual manifestations the most frequent is meconium ileus, intestinal obstruction in the newborn infant, due to the presence of inspissated meconium in the small intestine, which occurs in 10 per cent of the newborn with cystic fibrosis. Cirrhosis of the liver, sinusitis and other

complications will be mentioned later in this editorial.

Diagnosis of cystic fibrosis should be based on four criteria: increase in concentration of electrolyte in sweat, absence of pancreatic enzymes on assay of aspirated duodenal secretions, chronic pulmonary involvement (generalized obstructive emphysema and bilateral bronchopneumonia), and a family history of this disorder. The most widely used laboratory diagnostic procedure at the present time is the sweat test, because of its simplicity and reliability. In addition it is desirable to obtain a duodenal drainage for determination of trypsin, both as a confirmatory test and to further evaluate pancreatic function. It is important to realize two points: first, that one or more of these four criteria may be absent in the individual patient, two being usually sufficient for the diagnosis; and second, if an otherwise asymptomatic individual has an abnormal sweat test, he cannot be diagnosed as having the disease, cystic fibrosis, but is presumably a heterozygotic carrier, provided adrenal insufficiency is excluded.

Treatment consists primarily of antibiotic therapy for the chronic pulmonary involvement and has been reviewed by several authors. §, 10, 12 When

 <sup>&</sup>lt;sup>11</sup> di Sant'Agnese, P. A., Darling, R. C., Perera, G. A., and Shea, E.: Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas, Pediatrics 12: 549, 1953.
 <sup>12</sup> di Sant'Agnese, P. A.: Fibrocystic disease of the pancreas, a generalized disease of exocrine glands, J. A. M. A. 160: 846, 1956.

pancreatic deficiency is present, as is usually the case, some restriction in fat intake and pancreatic replacement therapy is desirable. Additional salt intake during hot weather is recommended as prophylaxis.

# III. Cystic Fibrosis in Young Adults (Patients with the Fully Manifested Syndrome: Homozygotes)

McIntosh, in 1954,18 reported an evaluation of patients over ten years of age with cystic fibrosis, dealing in part with the group of patients under consideration. With this exception little has as yet appeared in the literature concerning the older patients. It has been our experience that the disease differs somewhat at this age from that seen in infancy. Although nearly all have pancreatic deficiency, digestive symptoms are frequently minimal, clinical evidence of deficiency of fat-soluble vitamins is unusual, and most patients tolerate an almost unrestricted diet. The majority of older patients have chronic bronchitis, generalized obstructive emphysema and chronic sinusitis. The severity of the pulmonary manifestations varies widely. In rare individuals there is almost no pulmonary involvement at any time. Others are prone to chronic bronchitis and bronchopneumonia but appear to have no irreversible damage to the bronchial tree following response to antibiotic therapy, while in many the respiratory disease takes a progressive step-wise downhill course. Since all, or nearly all, lack pancreatic function and have abnormally high sweat electrolytes, the variations in clinical manifestations cannot be said to represent variations in severity of the underlying disease. However, those with less pulmonary involvement have a better prognosis for life and well being.

Brief case reports of three patients, all of whom were born in 1938 and

reached the age of 20 years, will help to clarify some of these points.

P.D.B., a 20-year-old white male, has no siblings and both father and mother are living and well. Ever since infancy he has been ravenously hungry and the stools always abnormal in character. He was first admitted to Babies Hospital at the age of 10 years for investigation of severe abdominal pains. He had never had any difficulties with his respiratory tract. An extensive study failed to provide an explanation for the abdominal pains which have not recurred since. A duodenal drainage at this time showed no tryptic activity in the duodenal contents. Balance studies revealed massive steatorrhea, with fecal loss of 40 grams of fat per 24 hours on a dietary intake of 70 grams. With some surprise at the findings, a diagnosis of cystic fibrosis was entertained. This was later confirmed by several other duodenal assays and by sweat tests.

Even when first admitted at the age of 10 years and despite the fact he had been on an unrestricted diet he was quite normal in height for his age, albeit a little thin. His dietary fat intake was subsequently restricted

<sup>&</sup>lt;sup>18</sup> McIntosh, R.: Cystic fibrosis of the pancreas in patients over 10 years of age, Acta pædiat. (Suppl. 100) 43: 469, 1954.

and pancreatic extracts were added by mouth. He has continued doing very well, his diet has been gradually liberalized and at the age of 20 years he is 175 cm. in height and 73 Kg. in weight. He has never suffered from serious respiratory infections, although once every one or two years he does have an acute bronchitis easily dominated by antibiotics. He goes to college, has won several fellowships and does night work on the side.

This patient is an example of fibrocystic disease with complete pancreatic deficiency and abnormally high sweat electrolytes, who has never had pulmonary involvement and as a consequence has done very well. It is interesting that on extensive pulmonary studies in 1954 14 even this boy

had a pathologic degree of retention of air in his alveoli.

V. D., a white male, 20 years of age, has one sibling living with cystic fibrosis and one other who died many years ago of the same disease. Three other siblings and the father and mother are living and well. His disease was identified as cystic fibrosis in 1943 on the basis of the family history, a drainage showing no tryptic activity of the duodenal contents, and the roentgenographic appearance of the chest. The diagnosis was later confirmed by sweat tests.

Throughout his childhood he had one respiratory infection after another, often complicated by otitis media. He was frequently ill and never completely free of coughing. Aureomycin became available at this time and in 1950 following continued administration of this drug, first in therapeutic and then in prophylactic dosage, he improved remarkably and gained 9 kilograms in a period of one and one-half years. Since then he has been essentially well, although never entirely free of minor respiratory symptoms. He has not been receiving antibiotics except when needed once or twice a year for one or two weeks at a time. His chest roentgenogram has shown remarkable improvement.

The character of the stools is not normal, but the patient refuses to follow any therapeutic regimen or to take pancreatin. He regularly smokes more than a pack of cigarettes a day. At the age of 20 years he is 168 cm. in height and 50 Kg. in weight. He does hard physical labor in a supermarket, has served some time in the National Guard, and his draft classi-

fication is now 1A.\* He is engaged to be married.

This patient is an example of fibrocystic disease in whom pulmonary involvement was never very severe and who has responded dramatically and

gratifyingly to antibiotic agents.

C. J., a white male, died of the pulmonary involvement of cystic fibrosis at the age of 20 years. Four other siblings and the mother are living and well. The father and a sister of the patient have some degree of chronic pulmonary involvement and elevated sweat electrolytes. The patient was

for military service under any circumstances.

West, J. R., Levin, S. M., and di Sant'Agnese, P. A.: Pulmonary function in cystic fibrosis of the pancreas, Pediatrics 13: 155, 1954.
 \*In our judgment no patient with cystic fibrosis of the pancreas should be accepted.

diagnosed as having cystic fibrosis in 1940 at the age of 16 months on the basis of the clinical and roentgenographic picture and a drainage showing no tryptic activity of the duodenal contents. The diagnosis was confirmed

by repeated sweat tests when they became available.

The patient was kept on a diet low in fat and high in protein content, and pancreatic extracts were consistently given by mouth. He was virtually never off antibiotics ever since they became available and frequently received courses of intensive therapy with drugs administered by intramuscular injection, by inhalation and by mouth. Despite this, through the years the severity of the pulmonary involvement increased, aggravated by overwork on the part of the patient. He was employed as a secretary in the first few years, but even this proved to involve too much exertion and he had to be hospitalized for treatment at frequent intervals. On December 12, 1958, during a relapse of the pulmonary infection, he died rather suddenly.

The patient is an example of failure of the antibiotics to control the respiratory infection, although they undoubtedly contributed to prolong his

life span.

The clinical picture of the adolescent or young adult with cystic fibrosis

has been gradually emerging.

The total number of patients with cystic fibrosis seen at Babies Hospital from 1939 through 1958 is 550. Of these 106 survived beyond the age of 10 years, the oldest is 24 years, and 85 of them are now living. As a group the older patients are doing better than the younger ones, perhaps because they would not have survived to a fairly old age unless the respiratory manifestations had been relatively mild. This statement, of course, does not apply to the individual patient.

The pulmonary involvement determines both their morbidity and their life expectancy. We know of only two patients who can be said never to have had chronic respiratory involvement. In many of the others it is rela-

tively mild and under satisfactory control with antibiotic agents.

All of the patients older than 13 years who are under observation at the present time have complete pancreatic exocrine deficiency. They appear to need less and less dietary restriction and pancreatic replacement therapy with advancing age. This again does not apply to the individual patient, but is true of the group as a whole. Several of our adolescent or young adult patients will not follow any prescribed regime and subsist on an average normal diet, and some do not take pancreatic extracts or vitamin supplements, yet despite this they usually seem to do well from a nutritional standpoint.

In agreement with the fact that the digestion and absorption of food seems more efficient with advancing age, the appetite, so characteristically ravenous in young children, decreases towards much more normal levels

in the older age group.

In patients with onset of symptoms in early life, retardation of growth has traditionally been part of the picture in cystic fibrosis, an arrest in

growth not entirely explained by dietary deficiency. However, when the onset of symptoms is delayed or when the respiratory infection has been well controlled, growth may for a time progress normally. In these children the prepuberal growth spurt tends to be delayed. A common story is that the child was average in height until about ten years of age. He failed to show the usual adolescent growth spurt and by fourteen was the shortest in his class. However, two or three years later, he was of low average adult height.

Sexual maturation has proceeded normally, although at times delayed somewhat, even in the patients more severely affected from the standpoint

of the chronic lung involvement.

In genetic parlance the gene for cystic fibrosis in double dose or homozygous condition is semi-lethal; that is, the great majority of similarly affected patients will die before they reach the reproductive stage, but very occasional individuals will live long enough to marry and have children. Up to the present, few patients (such as our patient P. D. B.) who present all or most of the manifestations of the disease have lived beyond early adult life.

The psychological impact of the publicity given to the disease and to its more lethal aspects in lay magazines and newspapers in order to raise money for the otherwise praiseworthy cause of further research into this obscure disorder has been of increasing concern in the adolescent and young adult patients with cystic fibrosis.

Complications of cystic fibrosis more common in young adults than in infants. Certain complications, although not unknown among children with cystic fibrosis, are seen with greater frequency in young adults with this disease. These manifestations may be listed as follows in decreasing

order of frequency.

- 1. Sinusitis. Involvement of the paranasal sinuses is a regular and expected finding on roentgenographic examination. However, it appears to give rise to clinical symptoms mainly in the older age group. This is due partly to the progressive pneumatization of the sinuses with age, leading them to play a much greater role in later childhood and young adult life. A nasal voice, post-nasal drip and polyps, generally necessitating surgical removal and recurring after some time, are frequently seen in such patients. No specific treatment directed to the paranasal sinuses is usually needed. It is part of the respiratory involvement in cystic fibrosis and responds best to the antibiotic treatment which is administered for the pulmonary disease.
- 2. Hemoptysis and spontaneous pneumothorax. Hemoptysis has been observed in six patients and spontaneous pneumothorax in three additional ones. Both of these manifestations have recurred several times in the same individuals and all of the patients have been in the older age group. These well known complications of chronic pulmonary disease have sometimes been difficult to dominate at the time they occurred, but they are an un-

favorable prognostic sign implying serious and progressive pulmonary involvement.

3. Cirrhosis of the liver with portal hypertension. The multilobular biliary cirrhosis, a pathologic picture distinctive of cystic fibrosis, has been described in detail elsewhere. Although the initial lesions found at autopsy in a large percentage of patients with fibrocystic disease do not give rise to clinical symptoms, after years of destruction and regeneration of the parenchyma of the liver, the hepatic architecture in some cases becomes so distorted as to lead to portal hypertension with ascites, hypersplenism, massive gastrointestinal hemorrhage or a combination thereof. While this clinical picture may occasionally be seen in relatively small children, it is found more frequently in older patients.

4. Appendiceal abscesses and abdominal masses. Abdominal masses, usually of a relatively small size and located in the right lower quadrant, are not infrequent at all ages. Some of these have been explored surgically and shown to be fecal in origin. Unless they give rise to obstructive or other symptoms no treatment is needed and the masses are usually passed

spontaneously after days or weeks.

Appendiceal abscesses with symptoms masked by the continuous administration of antibiotics for the pulmonary involvement have been seen in two patients, aged 4 years and 19 years, respectively. It is not a common complication but one important to keep in mind, because of its impli-

cations. Both of these patients recovered after operation.

5. Diabetes mellitus. Diabetes mellitus has been encountered in only two of the total series of 550 patients. In one of them there was a family history of diabetes mellitus. However, in both of these patients, 10 years and 13 years of age respectively, there were multiple flecks of calcification in the pancreas on roentgenographic examination of the abdomen, a most unusual finding in this disease. It is possible to speculate that diabetes mellitus with or without pancreatic calcification may be encountered more frequently as the average age of the patients increases.

# IV. Individuals Presenting Only Some of the Manifestations of Cystic Fibrosis (Heterozygotes)

Up to the present we have spoken of patients presenting all or most of the manifestations of the syndrome of cystic fibrosis, homozygotes according to the hypothesis of a recessive transmission. This hypothesis assumes the existence of heterozygotes among parents, some of the siblings of patients, and some individuals from families in which by chance no cases of cystic fibrosis have been recognized. Do these heterozygotes bear any stigmata of the disease? Investigations along these lines are in the initial phase, and precise knowledge of these matters has not yet been established.

<sup>&</sup>lt;sup>15</sup> di Sant'Agnese, P. A., and Blanc, W. A.: A distinctive type of biliary cirrhosis of the liver associated with cystic fibrosis of the pancreas: recognition through the signs of portal hypertension, Pediatrics 18: 387, 1956.

1. Known or probable heterozygotes. If cystic fibrosis is transmitted as a recessive character and its incidence estimated at 1 per 1,000 live births. it then follows from the laws of genetics that about 1 in 20 of the population must carry the recessive gene. This may seem to be an excessively high figure to those of us who are not initiated in genetic lore. However, it has been repeatedly shown that natural populations are replete with deleterious recessive mutants concealed in the heterozygous condition by their normal alleles.16

It has been recognized with increasing frequency in the last few years that in many genetically transmitted pathologic conditions the heterozygotes may have some manifestation of the trait (e.g., in sickle cell anemia or Mediterranean anemia). So far, no stigmata are present in all individuals presumed to be heterozygotes for the gene concerned with cystic fibrosis. However, from 20 to 30 per cent of relatives (both children and adults) of index cases have sweat electrolyte levels elevated above the normal values.7 There are usually no other manifestations of the syndrome, although a tendency to frequent respiratory infection and attacks of so-called "asthma" are not uncommon and more severe respiratory involvement characterized by generalized obstructive emphysema is also seen at times in relatives of patients known to have cystic fibrosis.

Recent investigations, still in the preliminary stage, have shown that the behavior of sweat electrolytes in response to various types of stress (salt restriction, heat, administration of adrenocortical hormones) is different at least in some individuals presumed to be heterozygous as compared with the homozygotes. Whereas the latter cannot conserve salt via their sweat glands in the presence of normal renal and adrenal function, the former instead, at least in the cases studied so far, are able to conserve salt in this secretion in response to stress, even though their sweat electrolyte concentration is apt to rise at times to abnormally high levels. In view of these findings it is possible that some of the heterozygous individuals who present normal sweat electrolyte values when first tested, may show abnormal levels of chloride and sodium in this secretion under different circumstances and at different times.

If it is assumed that individuals heterozygotic for cystic fibrosis represent 5 per cent of the population and that one in four of these have an abnormal concentration of sweat electrolytes, one can expect 1.25 per cent of the population to have a high sweat test. This is exemplified by the repeated experience in many hospitals that at least one among the volunteer student nurses or resident physicians used as controls in sweat analysis has turned out to have a positive test, although otherwise asymptomatic.

2. The sweat test in adult patients with generalized obstructive emphysema. In recent investigations by Wood and associates, <sup>17</sup> 5 of 24 patients,

<sup>&</sup>lt;sup>16</sup> Sinnott, E. W., Dunn, L. L., and Dobzhansky, T.: Principles of genetics, 1958, McGraw-Hill Book Co., Inc., New York.
<sup>17</sup> Wood, J. A., Fishman, A. P., Reemstma, K., Barker, H. G., and di Sant'Agnese, P. A.: A comparison of sweat chlorides and intestinal fat absorption in chronic obstructive emphysema and fibrocystic disease of the pancreas, New England J. Med., in press.

21 to 86 years of age, with generalized obstructive emphysema have been found to have elevated sweat electrolytes. All of these subjects were demonstrated not to have adrenal insufficiency. In all of them tryptic activity of duodenal contents was normal and in none was there a family history of cystic fibrosis. Despite the absence of these other confirmatory findings it is thought possible that these patients might in reality fall in the category of individuals with only partially manifested fibrocystic disease, since to date no other disorders have been found (with the exception of Addison's disease) in which the sweat test is abnormal. These include other varieties of chronic pulmonary disease among many conditions which have been investigated.

## SUMMARY AND CONCLUSIONS

Cystic fibrosis of the pancreas was recognized as a separate disease entity 21 years ago, but it is only in the last 10 years that most of the patients have been diagnosed. Pulmonary involvement dominates the clinical picture and determines the fate of the patient. The advent of effective antibiotic agents has been responsible for greatly increasing the life span of many affected individuals, who now frequently reach young adult age.

Cystic fibrosis of the pancreas, despite its name, is a generalized disease genetically determined and probably transmitted as a recessive trait. Homozygotes have the fully expressed syndrome with all or most of the clinical manifestations, including elevated sweat electrolytes. Their ultimate prognosis is guarded and it is not probable that many of these patients will have a normal life span. Twenty to thirty per cent of heterozygotes (children and adults) present as the only expression of the disorder an abnormally elevated concentration of sodium and chloride in their sweat. In addition a significant number of relatives of index cases have frequent attacks of bronchitis and are subject to so-called "asthma," while a smaller number suffer from more severe chronic respiratory involvement.

Much further study is needed to clarify the problems outlined and to interpret the facts brought to light by recent investigations. It is evident, however, that cystic fibrosis in the homozygous and heterozygous state and its possible relation to other types of chronic pulmonary disease presents a problem of increasing importance to the internists and to the specialist in chest disorders. Cystic fibrosis is breaking out of the pediatric bounds to which it had earlier been limited by its high mortality rate in infancy and childhood. It is now invading the domain of diseases of the adult individual.

Paul A. di Sant'Agnese, M.D. and Dorothy H. Andersen, M.D.

# REVIEWS

The Kidney. By H. E. de Wardener, M.B.E., M.D., F.R.C.P. 338 pages; 24.5 × 16 cm. Little, Brown and Company, Boston. 1958. Price, \$10.00.

The preface to this book volunteers the information that it was written for the medical student. It is impossible not to feel that there is too much detail present for this type of reader when it is remembered that renal diseases comprise only a small part of medicine and that this book has over 300 pages. The contents would seem more appropriate for the practicing physician in internal medicine.

The opening chapters on renal physiology and anatomy are clear and most useful, and they clearly demonstrate the necessity of having a firm understanding of these basic facts before a full appreciation of renal disease is possible. Renal tuberculosis is not included in the text as the author regards it as a surgical condition. With the advent of antituberculosis chemotherapy, there is no more justification for regarding renal tuberculosis as a surgical condition than there is for thinking of pulmonary tuberculosis as a surgical condition.

Some of the author's opinions are frankly controversial. Doubt is cast on the principle of giving carbohydrate in the form of glucose in acute cortical necrosis in order to restrict protein breakdown. Therapy based on this principle has produced better results than any other method excluding the artificial kidney and when the latter is not available, it seems unwise to abandon this form of treatment until something better is found. The changes in the optic fundus found in hypertension are divided into arteriosclerotic retinopathy and hypertensive neuroretinopathy. In spite of knowing that this division is favored by Pickering in his authoritative monograph on hypertension, it is impossible not to cavil at the word "arteriosclerotic." It is used in so many different contexts and most commonly seems to apply to atheroma or medial sclerosis, and it therefore seems misplaced when applied to the retinal arterioles. Retinal changes are related more to the duration and elevation of the blood pressure than any other factor. Hypertensive encephalopathy is not a rare complication of acute nephritis in pediatric practice. The two suggested treatments of encephalopathy are systemic methonium compounds or intravenous barbiturates. Neither of these methods is really suitable for a child with encephalopathic fits. Subacute bacterial endocarditis causes lesions in the kidney other than the "allergic nephritis" described and some mention should have been made of these.

The final section deals with the common diuretics in use. Most drugs are known by the same name in Great Britain as in the U. S. A.; however, a notable exception is the mercurial diuretic known in Britain as Mersalyl. In a book written in the U. S. A. by a British author, surely the U. S. P. name for Mersalyl could be included. Many complications of the mercurial diuretics are given attention, but neither the low salt syndrome nor hypochloremic alkalosis figure and both are important.

There is, in spite of what is said above, a definite place for this book and it should prove of assistance to many physicians practicing internal medicine who want a more detailed account of renal disease than is obtainable in the usual medical textbook.

Chloromycetin (Chloramphenicol). Antibiotics Monographs No. 8. By Theodore E. Woodward, M.D., and Charles L. Wisseman, Jr., M.D. 159 pages; 16 × 23.5 cm. Medical Encyclopedia, Inc., New York. 1958. Price, \$4.00.

This book is a summary of the clinical experience with one of the most widely used and most potent antibiotics, Chloromycetin. Written by two well-known authorities in the field of antibiotic chemotherapy, it is a lucid and eminently objective evaluation of the clinical status of this antibiotic. As might be expected, the chapters dealing with diseases in which the widest experience with Chloromycetin has been accumulated, such as the rickettsioses and typhoid fever, are the most informative. However, even in situations where the value of Chloromycetin is less clearly established, there is a concise discussion of the issues and the reader is encouraged to draw his own conclusions. The chapter on staphylococcal infections is particularly well-written and concerns itself more with the epidemiologic and clinical aspects of the problem than with its chemotherapy. On the other hand, the chapter on urinary tract infections is sketchy at best, and much more could have been said about the use of Chloromycetin in refractory infections of the genito-urinary system.

The authors emphasize that Chloromycetin has often not been used in optimum dosage, a fact not generally appreciated by the medical profession, who have tended to employ the same dosage levels for this agent as for the tetracyclines. These practical aspects are stressed throughout the book and make it a useful guide to the practicing physician. The bibliography is extensive, encompassing some 738 references, and reasonably up-to-date; the index is adequate. The book is a valuable contribution to the literature on antibiotics, and can be recommended to both practitioner and academician.

ROBERT G. PETERSDORF, M.D.

Fibroses Pulmonaires et Insuffisances Respiratoires Chroniques. By P. LAVAL and collaborators. 293 pages; 17 × 25 cm. (paper-bound). Masson et Cie, Paris. 1958. Price, 3.500 fr.

Chronic respiratory insufficiency is the end stage of many diverse processes which involve the lung and its airways. Professeur Laval and his colleagues of la Faculte de Medecine de Marseille have given broad treatment to this complex problem. In a monograph whose scope is much wider than might be inferred from its title, they deal with pathogenic factors, normal and altered pulmonary physiology, diagnostic procedures, clinical descriptions, and the results of various treatment programs. Endocrine factors and body morphology are given more emphasis than one usually encounters in American works on the subject. The section devoted to physiology, comprising about 30% of the book, is simply written. Alveolar ventilation and oxygenation of blood, oxygen transport mechanisms, and tissue respiration are each covered in the analysis of oxygen utilization. A chapter is devoted to carbon dioxide metabolism and the derangements caused by ventilatory insufficiency.

Technical aspects of pulmonary function testing are barely alluded to, and there is little mathematical treatment of methods of analyzing respiratory function. Mechanics of breathing are mentioned in passing, but no significant discussion of this important feature of respiratory physiology is attempted.

The reviewer found the monograph stimulating and comprehensive. Clear, concise writing style, simple language, and an interesting over-all approach make this book of value to all students of chronic lung diseases.

JEROME E. COHN, M.D.

Readings in Medical Care. Edited by the Committee on Medical Care Teaching of the Association of Teachers of Preventive Medicine. 708 pages; 16 × 24.5 cm. The University of North Carolina Press, Chapel Hill. 1958. Price, \$6.50.

This volume was prepared to provide teaching material on the organization of medical care. The various facets of medical care organization are sequentially arranged in chapter form and include the following topics: Problems in Medical Care, the General Background; The National Health Picture; Adequacy of Medical Care; The Costs of Medical Care; The Medical Care Team; Hospital; Coordination in Health and Medical Service; Care of Long-term Illness; Rural Medical Care; Public Medical Care; Medical Care in Industry; Medical Care Insurance; Principles and Proposals. Each chapter contains a number of selections on the subject matter of the chapter and divergent opinions on controversial subjects are well covered. Specific chapters and sections can be studied profitably without reference to other chapters.

The Committee on Medical Care Teaching is to be commended on the organization and the selection of the text material. It is, however, much more than a reference book on medical care organization, for it has a wealth of data and information on medical care, not only for teachers but also for all physicians concerned with the economic and social forces affecting medical care both at present and in the future.

GEORGE ENTWISLE, M.D.

Elements of Biophysics. By James E. Randall, B.S.E.E., M.S., Ph.D. 333 pages; 14 × 20.5 cm. The Year Book Publishers, Inc., Chicago, Illinois. 1958. Price, \$8,00.

Most physicians regard biophysics as an esoteric subject understood only by certain members of a group of other people. The subject is so formidable as to discourage all attempts at learning. It abounds with integral signs, mathematical formulae, incomprehensible graphs and above all it is without practical significance.

In this very remarkable little book Dr. Randall presents the *Elements* of Biophysics in a form and in a way that can be understood by anyone with an interest. He assumes very little prior knowledge of mathematics, physics or chemistry, begins with very elemental concepts and progresses through the field as he conceives it to be. Whenever possible a concept is illustrated by an example taken from medicine or biology.

Although the book's content—which is limited to Elements—is excellent, its greatest value will derive from the way it is written—Dr. Randall can explain difficult subjects with simple, lucid language.

A partial list of areas covered includes: basic concepts—mathematics, physics, statistics, measurements and instrumentation; mechanics; acoustics; electricity and electromagnetism; fluid statics and dynamics; atomic and nuclear physics. For the reviewer these are presented so as to be always profitable, frequently exciting and never tedious.

B. W. A.

Cardiovascular Diseases. By DAVID SCHERF, M.D., F.A.C.P., Professor of Clinical Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, New York; and LINN J. BOYD, M.D., F.A.C.P., Professor and Director of Medicine,

New York Medical College, Flower and Fifth Avenue Hospitals. 829 pages; 17.5 × 25 cm. Grune & Stratton, New York. 1958. Price, \$17.75.

This is the third English-language edition of this book which was originally published ten years ago. The entire text has been thoroughly revised and new sections have been added.

The authors emphasize a clinical approach, stressing physical examination rather than instrumental and laboratory methods. As is stated in the preface "A thorough analysis of the individual symptoms and physical findings, it seems to us, will permit a better evaluation of the situation which may be encountered at operation than will cardiac catherization and analysis of intracardiac pressure curves."

The initial chapters are devoted to dyspnea, hypertrophy and dilatation of cardiac chambers, percussion and auscultation, compensation and decompensation, with subsequent chapters on specific disease entities. In the last chapter, emphasis is placed upon various measures in cardiac therapy. There is an excellent bibliography after each chapter.

The authors comment on specific entities and therapeutic problems from the advantage of many years of competent experience. Their views are of considerable interest and are at times challenging. This text should be of value to students and to all physicians interested in cardiovascular diseases.

L. S.

Tumors of the Skin. (Atlas of Tumor Pathology, Section I—Fascicle 2.) By Herbert Z. Lund, M.D. 330 pages; 20 × 26 cm. (paper-bound). Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council, Washington, D. C. 1957. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C. at \$3.00.

The Fascicle on *Tumors of the Skin* by Dr. Herbert Z. Lund published by the Armed Forces Institute of Pathology is a fitting addition to the outstanding collection already assembled. It suffers from some of the same shortcomings of the series as a whole with the lack of any satisfactory index but merely an outline of the contents according to the author's classification of skin tumors or tumor-like conditions.

The book is particularly recommended to dermatologists for its brief but commendable discussion of nomenclature. It seems quite incongruous, after arriving at the logical conclusion that the term nevus should be restricted to lesions composed of nevus cells, that this fascicle should then fail to deal with either nevi or their malignant counterpart, the melanomas. The author keeps true to his promise that "in this fascicle the use of the word nevus . . . is avoided as much as possible."

The microphotographs are generally of good caliber but occasionally the technical flaws in the preparation of the material are all too clear. A number of the gross photographs fail to reach satisfactory quality, usually lacking depth of focus. The illustration of the turban tumor on page 93 produces distinctly uncoördinated fasciculation of the ocular muscles.

The fine distinctions between some of the basal cell and skin appendage tumors seem somewhat erudite at times but the peak is reached when an "intermediary cell carcinoma" of the skin appears as a classification. I agree with the author that this is "probably an unnecessary subdivision."

An outstanding section of the fascicle is the discussion of the histogenesis of chronic roentgen-ray dermatosis. This alone would be worth the price of the fascicle.

One cannot afford to pass up the opportunity to purchase such an excellent reference which offers a well chosen bibliography for those who are not satisfied with the synopsis treatment necessary in the fascicles.

HARLAN I. FIRMINGER, M.D.

## BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Acute Conditions: Incidence and Associated Disability, United States, July 1957–June 1958. Statistics on Incidence of Acute Conditions and Number of Associated Restricted-Activity Days, Bed-Days, Work-Loss Days, and School-Loss Days According to Condition Group. Health Statistics from the U. S. National Health Survey, Public Health Service Publication No. 584–B6. 47 pages; 26 × 20 cm. (paper-bound). 1958. U. S. Department of Health, Education, and Welfare, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, for 35¢.
- L'Année Thérapeutique: Médications et Procédés Nouveaux. Par A. RAVINA. 212 pages; 21.5 × 13.5 cm. (paper-bound). 1958. Masson et Cie, Paris. Price, 1.600 fr.
- The Central Nervous System and Behavior: Transactions of the First Conference, February 23, 24, 25, and 26, 1958. Edited by Mary A. B. Brazier, Ph.D., Neurophysiological Laboratory, Massachusetts General Hospital, Boston, Massachusetts. 450 pages; 23.5 × 16 cm. 1959. Sponsored by the Josiah Macy, Jr. Foundation, New York, with the coöperation of The National Science Foundation, Washington, D. C. Price, \$5.25.
- A Clinical Introduction to Heart Disease. By Crighton Bramwell, M.A., M.D., F.R.C.P., Emeritus Professor of Cardiology, formerly Professor of Systematic Medicine in the University of Manchester, etc. 229 pages; 22.5 × 14.5 cm. 1959. Oxford University Press, New York. Price, \$5.50.
- A Color Atlas of Morphologic Hematology, With a Guide to Clinical Interpretation.

  Revised Edition. By Geneva A. Daland, B.S., Chief Laboratory Assistant in Hematology, Thorndike Memorial Laboratory, etc.; edited by Thomas Hale Ham, M.D., Professor of Medicine and Chairman of the Committee on Medical Education, Western Reserve University, School of Medicine, Cleveland, Ohio; illustrations by Etta Piotti. 72 pages and 16 plates; 28 × 21 cm. 1959. Harvard University Press, Cambridge. Price, \$6.75.
- La Corticothérapie Surrénale dans le Traitement de la Tuberculose. Par MM. Ch. Gernez-Rieux, H. Warembourg et M. Pauchant. 216 pages; 25.5 × 17 cm. (paper-bound). 1958. Masson et Cie, Paris. Price, 2.600 fr.
- Cours Supérieur d'Anesthésie. Tome VII, 1958. Acta de l'Institut d'Anesthésiologie.

  Sous la direction de MM. les Professeurs P. Moulonguet et J. Baumann.

  268 pages; 24 × 15.5 cm. (paper-bound). 1958. Librairie Arnette, Paris.

  Price, 2.500 fr.
- Current Therapy-1959. Edited by Howard F. Conn, M.D.; Consulting Editors: George E. Burch, M. Edward David, Vincent J. Derbes, Garfield G. Dun-

- CAN, HUGH J. JEWETT, CLARENCE S. LIVINGOOD, PERRIN H. LONG, H. HOUSTON MERRITT, WALTER L. PALMER, HOBART A. REIMANN, CYRUS C. STURGIS and ROBERT H. WILLIAMS. 781 pages; 27.5 × 20.5 cm. 1959. W. B. Saunders Company, Philadelphia. Price, \$12.00.
- Diffuse Lesions of the Stomach: An Account with Special Reference to the Value of Gastric Biopsy. By Ian J. Wood, M.D. (Melbourne), F.R.C.P., F.R.A.C.P., Assistant Director of the Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, etc.; and Leon I. Taft, M.B., B.S., B.Sc. (Melbourne), Pathologist to the Clinical Research Unit of the Royal Melbourne Hospital and Walter and Eliza Hall Institute, Melbourne, Victoria, Australia. 86 pages; 22.5 × 14.5 cm. 1958. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, \$6.00.
- Diseases of the Colon and Anorectum. Volumes One and Two. Edited by ROBERT TURELL, M.D., Associate Surgeon and Chief, Rectal Clinic, The Mount Sinai and Montefiore Hospitals, etc. 1,238 pages (both volumes); 26.5 × 17.5 cm. 1959. W. B. Saunders Company, Philadelphia. Price, \$35 per set.
- Don't Worry About Your Heart. By Edward Weiss, M.D. 203 pages; 21 × 14 cm. 1959. Random House, New York, Price, \$3.95.
- The Family Medical Encyclopedia. A Health Education Council Book. By Justus J. Schifferes, Ph.D.; illustrated by Louise Bush, Ph.D. 617 pages; 19.5 × 13 cm. 1959. Little, Brown and Company, Boston. Price, \$4.95.
- La Fièvre Typhoïde: Étude Critique d'Épidémiologie Appliquée. Par MAURICE DEPARIS et RAYMOND ARDAILLOU. 224 pages; 25.5 × 17 cm. (paper-bound). 1958. Masson et Cie, Paris. Price, 2.300 fr.
- Help for Ten Million: A Manual for Patients with Arthritis, Rheumatism and Gout. By Darrell C. Crain, M.D., F.A.C.P., Clinical Associate Professor in Medicine, Georgetown University Medical School, Washington, D. C. 251 pages; 18.5 × 11 cm. (paper-bound). 1959. J. B. Lippincott Company, Philadelphia. Price, \$1.45.
- Highlights, National Conference on Air Pollution, 1958. Public Health Service Publication No. 648. 42 pages; 20.5 × 26.5 cm. (paper-bound). 1959. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by Superintendent of Documents, U. S. Government Printing Office, Washington, D. C., at 35¢.
- Hospitalization, Patients Discharged from Short-Stay Hospitals, United States, July 1957-June 1958. Statistics for Short-Stay Hospitals on Patients Discharged and Days of Hospitalization, by Selected Characteristics of the Patients, and Types of Hospitals. Based on Data Collected in Household Interviews During July 1957-June 1958. Public Health Service Publication No. 584-B7. 40 pages; 26.5 × 20 cm. (paper-bound). 1958. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C., at 30¢.
- Industrial Medicine in Western Pennsylvania, 1850–1950. By Dr. T. Lyle Hazlett and William W. Hummel. 301 pages; 23.5 × 15.5 cm. 1957. University of Pittsburgh Press, Pittsburgh. Price, \$6.00.

- Manual of Differential Diagnosis. By WILLIAM C. MATOUSEK, M.D., Chief, Medical Service, Veterans Administration Hospital, Miles City, Montana. 352 pages; 20.5 × 14 cm. 1959. The Year Book Publishers, Inc., Chicago. Price, \$8.00.
- Medicine for Nurses. 4th Ed. By M. Toohey, M.D., M.R.C.P., D.C.H., Physician, New End Hospital, London; with a chapter on Psychological Medicine by Henry R. Rollin, M.D., D.P.M., Psychiatrist, Horton Hospital, Epsom, and New End Hospital, London. 663 pages; 22 × 14 cm. 1959. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$7.00.
- Physical Diagnosis: The History and Examination of the Patient. By JOHN A. PRIOR, M.D., Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio; and JACK S. SILBERSTEIN, M.D., Clinical Associate Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio; and contributors. 388 pages; 25.5 × 17.5 cm. 1959. The C. V. Mosby Company, St. Louis. Price, \$7.50.
- Physiologie und Experimentelle Pathologie der Leber. Von Dr. Anton Fischer. 187 pages; 24.5 × 17.5 cm. 1959. Publishing House of the Hungarian Academy of Sciences, Budapest.
- The Plasma Proteins: Clinical Significance. By PAUL G. Well, B.A., M.D.C.M., M.Sc., Ph.D., Director, Transfusion Service and Assistant Physician, Royal Victoria Hospital, etc. 133 pages; 19 × 11.5 cm. 1959. J. B. Lippincott Company, Philadelphia. Price, \$3.50.
- Psychopharmacology Frontiers: Proceedings of the Psychopharmacology Symposium, Second International Congress of Psychiatry. Edited by NATHAN S. KLINE, M.D., Director of Research, Rockland State Hospital, Orangeburg, New York, etc. 533 pages; 24 × 16 cm. 1959. Little, Brown and Company, Boston. Price, \$10.00.
- The Psychosomatic Aspects of Internal Medicine. Transactions of the Fifth Annual Meeting of the Academy of Psychosomatic Medicine. Edited by Wilfred Dorfman, M.D., F.A.C.P. 268 pages; 25.5 × 17.5 cm. 1958. The Academy of Psychosomatic Medicine, Wilfred Dorfman, M.D., F.A.C.P., Editor, 1921 Newkirk Avenue, Brooklyn 26, N. Y. Price, \$3.00.
- Reminiscences and Adventures in Circulation Research. By CARL J. WIGGERS, M.D., Professor Emeritus of Physiology, Western Reserve University, School of Medicine, etc. 404 pages; 23.5 × 15.5 cm. 1958. Grune & Stratton, New York. Price, \$9.75.
- Staphylococcus Pyogenes and Its Relation to Disease. By Stephen D. Elek, M.D., D.Sc., Ph.D., D.P.H., Professor of Bacteriology in the University of London, etc. 767 pages; 24.5 × 16 cm. 1959. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$15.00.
- Surgery of the Sympathetic Nervous System. 3d Ed. By Professor Sir James Paterson Ross, K.C.V.O., LL.D., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., Director of the Surgical Professorial Unit, St. Bartholomew's Hospital, London. 170 pages; 24 × 16 cm. 1958. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$8.00.
- A Textbook of Neurology. 2nd Ed. Revised. By H. Houston Merritt, M.D., Professor of Neurology, Columbia University, etc. 765 pages; 24 × 16 cm. 1959. Lea & Febiger, Philadelphia. Price, \$12.50.

- Transactions, American Society for Artificial Internal Organs, Philadelphia, Pennsylvania, April 13-14, 1958. Vol. IV. Editor: George E. Schreiner, M.D. 258 pages; 28 × 22 cm. (loose-leaf, paper-bound). 1958. Printed by the Georgetown University Press for the A.S.A.I.O. Price, \$5.00; copies may be ordered from Dr. George E. Schreiner, Department of Medicine, Georgetown University Medical Center, Washington, D. C.
- Urology in Outline. By T. L. Chapman, Ch.M., F.R.C.S.(Eng.), F.R.F.P.S.(Glas.), Honorary Clinical Lecturer in Urology (University of Glasgow), and Urological Surgeon, Victoria Infirmary, Glasgow, etc. 176 pages; 23 × 16 cm. 1959. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$6.75.

## COLLEGE NEWS NOTES

BOOKS DONATED TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College gratefully acknowledges receipt of the following books from members of the College to the Memorial Library of Publications by Members of the College:

- Arthur L. Bloomfield, M.D., M.A.C.P., San Francisco, Calif., A. BIBLIOGRAPHY OF INTERNAL MEDICINE: COMMUNICABLE DISEASES, published by The University of Chicago Press, Chicago, Ill., 1958, 560 pages.
- Robert E. Eckardt, M.D., F.A.C.P., Linden, N. J., INDUSTRIAL CARCINOGENS, published by Grune & Stratton, New York, N. Y., and London, England, 1959, 164 pages
- Albert S. Hyman, M.D., F.A.C.P., New York, N. Y., PRACTICAL CARDIOLOGY, published by Landsberger Medical Books, Inc., New York, N. Y., 1958, 307
- Samuel A. Levine, M.D., F.A.C.P., Boston, Mass., CLINICAL HEART DISEASE, published by W. B. Saunders Co., Philadelphia, Pa., and London, England, 1958, 673 pages.

## New Life Members

The College acknowledges with pleasure the following new Life Members:

- Dr. Alexander Altschul, New York, N. Y.
- Dr. J. Richards Aurelius, St. Paul, Minn.
- Dr. David B. Carmichael, Jr., La Jolla, Calif.
- Dr. Charles D. Driscoll, West Collingswood, N. J.
- Dr. Wendell B. Gordon, Pittsburgh, Pa.
- Dr. John Lansbury, Philadelphia, Pa. Dr. Howard H. Montgomery, Washington, D. C.
- Dr. E. Burkett Reed, Lincoln, Nebr.
- Dr. Isidore L. Robbins, New Orleans, La.
- Dr. Hobart Rogers, Oakland, Calif.
- Dr. Victor E. Schulze, San Angelo, Tex.
- Dr. M. Stephen Schwartz, New York, N. Y.
- Dr. Leonard Shapiro, Brooklyn, N. Y.
- Dr. Carter Smith, Atlanta, Ga.
- Dr. Charles William Smith, Harrisburg, Pa.
- Dr. Max E. Suehs, Beaumont, Tex.
- Dr. Cornelius H. Traeger, New York, N. Y.

## COLLEGE FELLOWSHIPS AND SCHOLARSHIPS

## Research Fellowships in Internal Medicine and Pediatrics

The American College of Physicians offers a limited number of Fellowships in Medicine and Pediatrics for the period July 1, 1960–June 30, 1961. These Fellowships are designed to provide an opportunity for research training, either in the basic medical sciences, or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine.

Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

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The stipend will be from \$3,300.00 to \$5,000.00, depending on number of dependents.

## Traveling Scholarships

There are two A. Blaine Brower Traveling Scholarships. Each is intended to support a traveling or visiting scholarship and to provide an opportunity for worthy, young physicians, preferably Associates of the College, to spend a month, more or less, as visiting fellows at some institution, or institutions, for observation and post-graduate study. The Committee on Fellowships and Scholarships of the College facilitates opportunities for these scholarships at outstanding institutions where a month's observation, contact and study will be an exceptional inspiration and a practical source of training. The income, approximately \$400.00 each, is used for payment of travel expenses, in whole or in part. Recipients are chosen and institutions designated by the Committee on Fellowships and Scholarships, approved by the Board of Regents of the College.

The Elizabeth Archbold Bowes Traveling Scholarship, established through a grant by Mrs. Margaret Bowes Murphy, Chicago, Ill., in memory of her mother, is administered on the same bases as the Brower Traveling Scholarships, but is restricted to candidates from Canada.

The Willard O. Thompson Memorial Traveling Scholarship was established by the late Dr. Thompson's widow, Dr. Phebe Thompson, and by friends of Dr. Thompson. It is particularly directed toward the field of endocrinology, the specialty in which Dr. Thompson was most interested. It is administered on the same bases as the Brower Traveling Scholarships.

Associates of the College interested in the above scholarships should file application on or before October 15 each year; recipients will be selected by the Committee on Fellowships and Scholarships and the Board of Regents at their mid-November meeting. Scholarships will be arranged to start after the following January 1, at the convenience of the recipient and the preceptor or institution.

The Southern California Traveling Scholarship is in all respects similar to the Brower Traveling Scholarship except that it is restricted to Associates in Southern California. It is financed by the Southern California members of the College, and applications shall be made to the College Governor for Southern California, Dr. George C. Griffith, Los Angeles.

The Governor and his Committee will choose nominees and submit them to the Committee on Fellowships of the Board of Regents. All applications must be filed with the Governor by October 1, each year.

## Mead Johnson Postgraduate Scholarship Awards

The Mead Johnson Postgraduate Scholarships of The College consist of eight awards of \$1,000.00 each, annually. Recipients shall be individuals who intend to practice Internal Medicine, who appear to possess the attributes for success in that specialty and who need funds to help them attain their goal of adequate education in Internal Medicine. Awards are open to interns or residents, with some preference to residents. Applications must be made to the Executive Offices of the College by October 1 of each year; selections will be made in mid-November, the Scholarships to begin the following July 1.

## For Information

Those interested in securing more information regarding any of the Fellowship or Scholarship Programs should write to Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Registration

AMERICAN COLLEGE OF PHYSICIANS—REGIONAL MEETINGS 1958-59

Territory	City	Date	Governor (s)	Official Guest (8)	Mbrs.	Non- mbrs.	Total
1-Regional Meetings between 1958 & 1959 Annual Sessions, Spring and Autumn, 1958	n 1958 & 1959 Annual Se	ssions, Spring a	nd Autumn, 1958				
Northern California	San Francisco	June 18	Stacy R. Mettier	Dwight L. Wilbur, President	122	20	172
North Dakota	Fargo	Sept. 6	R. O. Goehl	Howard Wakefield, Regent	30	19	49
Michigan	Traverse City	Sept. 19-20	H. Marvin Pollard	Dwight L. Wilbur, President E. R. Loveland, Exec. Sec.	106	89	174
West Virginia	Huntington	Sept. 20	Paul H. Revercomb	Charles H. Drenckhahn, 3rd Vice President Maurice C. Pincoffs, Editor, ANNALS; Regent	33	20	53
Idaho-Utah	Sun Valley, Idaho	Sept. 27	Richard P. Howard T. C. Bauerlein	Chester S. Keefer, Regent	24	17	41
Midwest (III., Ind., Iowa, Minn., Wis.)	Milwaukee, Wis.	Sept. 27	F. W. Madison	Dwight L. Wilbur, President Howard P. Lewis, President-Elect E. R. Loveland, Exec. Sec.	228	159	387
Western New York	Syracuse	Oct. 3	John H. Talbott	Howard P. Lewis, President-Elect E. R. Loveland, Exec. Sec.	109	56	165
Southeastern (Ala., Fla., Ga., Miss., S. C., Cuba)	Biloxi, Miss.	Oct. 3-4	D. O. Wright	Dwight L. Wilbur, President	74	21	95
Montana-Wyoming	Casper, Wyo.	Oct. 10-11	Wayne Gordon	Philip S. Hench, Regent	18	7	25
New Mexico	Santa Fe	Oct. 11	Robert Friedenberg	Howard Wakefield, Regent	18	25	43

Registration

American College of Physicians—Regional Meetings (Continued) 1958–59

Territory	City	Date	Governor (s)	Official Guest (s)	Mbrs.	Non- mbrs.	Total
Arizona	Phoenix	Oct. 18	William R. Hewitt	Fuller B. Bailey, Regent	36	14	20
Arkansas-Oklahoma	Hot Springs, Ark.	Oct. 18	Bert F. Keltz John N. Compton	Dwight L. Wilbur, President	76	26	102
Kentucky-Tennessee	Louisville, Ky.	Oct. 18	Sam A. Overstreet Rudolph H. Kampmeier	Charles A. Doan, 1st Vice President	06	51	141
District of Columbia, Maryland, Delaware	Washington, D. C.	Nov. 1	Theodore J. Abernethy R. Carmichael Tilghman Ward W. Briggs	William S. Middleton, Past President	66	72	171
Eastern Canada & New England States (New Brunswick, Newfoundland, Nova Scotia, Quebec, Conn., Maine, Mass., N. H., R. I., Vt.)	Quebec, P. Q., Can.	Nov. 7-8	8 Walter deM. Scriver	Dwight L. Wilbur, President Paul L. Cotton, Exec. Asst.	125	36	181
New Jersey	Newark	Nov. 12	Edward C. Klein, Jr.	Dwight L. Wilbur, President G. Ray Higgins, Asst. Exec. Sec.	127	77	204
North Carolina	Winston-Salem	Dec. 4	Elbert L. Persons	Robert Wilson, Regent Wilburt C. Davison, F. A. C. P.	\$6	44	129
Puerto Rico San Juan II—Regional Meetings, Winter and Spring, 1959	San Juan r and Spring, 1959	Dec. 19-20	-20 F. Hernandez-Morales	Robert Wilson, Regent	20	40	99
Colorado	Colorado Springs	Jan. 16-17	-17 Constantine F. Kemper	Philip S. Hench, Regent	62	67	129
Ohio	Cincinnati	Jan. 22	A. Carleton Ernstene	Dwight L. Wilbur, President	98	53	151

Registration

AMERICAN COLLEGE OF PHYSICIANS—REGIONAL MEETINGS (Continued) 1958-59

					Name and Address of the Owner, where	-	-	
Territory	City	Date	Governor (s)	Official Guest (s)	Mbrs.	Non- mbrs.	Total	
Eastern Pennsylvania	Philadelphia	Jan. 23	William A. Jeffers	Dwight L. Wilbur, President	260	142	402	
Prairie (Alberta, Manitoba, Saskatchewan)	Banff, Alta., Can.	Jan. 29	Percy H. Sprague Francis A. L. Mathewson	Fuller B. Bailey, Regent	18	12	30	
Western Pennsylvania	Pittsburgh	Feb. 4	Frank J. Gregg	Charles A. Doan,	57	19	92	
Southern California	Palm Springs	Feb. 7-8	George C. Griffith	Dwight L. Wilbur, President Howard P. Lewis, President-Elect	225	97	322	
Pacific Northwest (B. C., Ore., Wash.)	Vancouver, B. C., Can.	Feb. 14	H. Archibald Des Brisay	Howard P. Lewis, President-Elect	26	6	65	
Louisiana-Mississippi	Jackson, Miss.	Feb. 20	Laurance J. Clark Marion D. Hargrove	Robert Wilson, Regent	36	12	84	
Missouri	Kansas City	Feb. 21	Carl V. Moore	Dwight L. Wilbur, President	19	28	92	
Hawaii	Honolulu	Feb. 25	Hastings H. Walker	H. M. Pollard, F. A. C. P. Joseph F. Borg, F. A. C. P.	30	63	93	
Nebraska	Omaha	Mar. 7	Edmond M. Walsh	Dwight L. Wilbur, President	47	18	65	
Kansas	Wichita	Mar. 20	Fred J. McEwen	William C. Menninger, Regent	09	77	137	
Virginia	Hot Springs	Mar. 21	Charles M. Caravati	Dwight L. Wilbur, President	29	18	90 10	

## AMERICAN COLLEGE OF PHYSICIANS RESIDENCY REVOLVING LOAN FUND

The American College of Physicians has funds available to support a limited program of loans to those physicians who require financial assistance during their residency training. The purpose of the loans is to aid young physicians planning a future career in Internal Medicine, or specialties allied thereto, to pursue adequate graduate training as full-time residents, research assistants and/or fellows in accredited institutions, which training might otherwise not be available to them because of financial needs. The Committee may give some priority to candidates anticipating careers in academic medicine, although that shall not be a requirement.

The rules and regulations governing the loans are: (1) Loans shall be restricted to full-time medical residents, fellows in training in accredited institutions and research assistants—citizens of the United States, its dependencies, or Canada; (2) Loans shall be limited to not more than \$1,000.00; such loans shall be made only for living expenses incidental to the period of training; (3) Loans may be made for varying periods of time, up to a maximum of five years, but may be repaid in part or in full at any time; (4) No interest shall be charged for the first two years of the loan, or until completion of specialty training, whichever comes first: thereafter simple interest shall be charged at the rate of 3% per annum for two years: 6% thereafter. It is anticipated that loans shall be completely repaid by the end of five years. Any loan not completely repaid shall be declared in default and subject to such penalties that may be determined by the Committee; (5) Application shall be made on the official form supplied by the College; (6) When the application is approved by the Committee, the borrower shall sign the official, non-negotiable contract form supplied by the College; co-signed by the wife, parent or guardian; (7) All repayments and interest on loans shall be returned to the Residency Revolving Loan Fund, thus to perpetuate the Fund and its benefits for the future: (8) The College must be notified of change in address during period of loan; also permanent address of a person or relative through whom contact may be made at all times.

For information and application forms write to the American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

## AMERICAN COLLEGE OF PHYSICIANS DIRECTORY

The new, revised Directory of the American College of Physicians will be published during the fall of 1959. The last complete Directory was published in 1955.

All members of the College will receive a special form which, when filled out and returned, will provide the editors with the information to be included in the Directory. The biographical index will include: name in full, primary specialty, sub-specialty, degrees, office address, home address, year of birth, medical school and date of graduation, important present appointments, record of certification, and date of election to the College.

Members are urged to fill out the forms fully and return them promptly to the College Headquarters. Any changes in location or in appointments which occur after the form is returned and before the publication of the Directory (anticipated November 1), should be reported immediately to the College Office.

## FELLOWSHIPS IN PEDIATRIC PSYCHIATRY

Two fellowships are available at the State University of New York College of Medicine in New York City for training in pediatric psychiatry. The fellowships are one year in duration and the stipend depends upon the extent of training. They have been established to give a physician who has training in pediatrics, a year's

experience in psychiatric aspects of pediatric practice. Fellows may begin their training on July 1, 1959, or thereafter. Candidates must be citizens of the United States or have declared their intention to become citizens. The Fellow will have an opportunity to participate in the research program of the Pediatric Psychiatry Unit, which currently is concerned with long-range developmental studies of prematurely born children, brain damage and the biologic aspects of mental illness. For information write to: Richard L. Day, M.D., Professor of Pediatrics, State University of New York College of Medicine at New York City, 451 Clarkson Ave., Brooklyn 3, N. Y.

## FELLOWSHIP FOR STUDY OF PITUITARY IRRADIATION

A fellowship for training in pituitary irradiation is available at the Donner Laboratory, University of California, in Berkeley, Calif. Fellowship will begin July 1 for one year and may extend for an additional year. The fellow will participate in a program utilizing a high-energy particle beam to study the effects of pituitary irradiation on various disease conditions including breast carcinoma and advanced diabetes mellitus. Also included will be training in the use of isotopes in diagnosis, therapy and research investigations.

Applicants must have had residency training in metabolism-endocrinology, radiology, or hematology. For information write Dr. John H. Lawrence, Director, Donner Laboratory, University of California, Berkeley 4, Calif. Inquiries should be accompanied by a complete curriculum vitae.

## OPPORTUNITIES FOR MEDICAL OFFICERS WITH THE FEDERAL GOVERNMENT

The United States Civil Service Commission recently announced the opportunities available to Medical Officers in the United States and foreign countries. Examinations will select physicians to fill positions in the following Federal services: The National Institutes of Health; Army, Navy, and Air Forces Installations (civilian service); Public Health Service; St. Elizabeths Hospital (Washington, D. C.); Indian Service Hospitals; Food and Drug Administration, and Children's Bureau.

Candidates must be graduates of a medical school of recognized standing with the degree of Doctor of Medicine and have completed an approved rotating internship and be currently licensed to practice medicine and surgery in a state or territory of the United States. For all fields of medicine except administration, general medicine and surgery, applicants must have had a full straight internship or residency or one year of postgraduate study in the field for which he applies. They must also be citizens of the United States and physically able to do the work involved in these positions.

For information write the United States Civil Service Commission, Washington 25, D. C.

## 2ND SUMMER INSTITUTE ON MEDICAL TEACHING

The 2nd Summer Institute on Medical Teaching jointly sponsored by the University of Buffalo School of Medicine and the Association of American Medical Colleges will be held in Buffalo, June 9–18, 1959. The Institute will provide an opportunity for medical instructors to join specialists in Education in an examination of teaching and learning in medical schools. Included in the presentations, demonstrations and discussions led by University of Buffalo faculty from the Schools of

Medicine, Education and Arts and Science, will be such topics as: the nature of learning; the nature of medical students and medical faculties; the philosophical background for higher education in the United States; the use of lecture and laboratory, ward exercise and clinical conference, as well as less familiar methods of instruction; the use of tests and other appraisal devices for measuring student performance in a Medical School. Opportunity for consultation on individual instructional problems will also be provided.

Attendance at the Institute will be limited. Interested members of Medical School faculties in the United States and Canada may apply for registration. For further information write to Dr. George E. Miller, Associate Professor of Medicine,

University of Buffalo School of Medicine, Buffalo 14, N. Y.

## 66TH ANNUAL CONVENTION OF THE ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The 66th Annual Convention of the Association of Military Surgeons of the United States will be held at the Mayflower Hotel, Washington, D. C., November 9-11, 1959. For information write to the Association of Military Surgeons of the United States, Suite 718, New Medical Bldg., 1726 Eye St., N. W., Washington 6, D. C.

## 1st International Symposium on Anti-Infectious and Antimitotic Chemotherapy

The 1st International Symposium on Anti-Infectious and Antimitotic Chemotherapy will be held in Geneva, Switzerland, September 12–13, 1959, under the Honorary Presidency of Professors E. B. Chain, D. Bovet and S. A. Waksman, and under the Presidency of Professor G. Bickel. The program will include reports and panel discussions, problems of high actuality: (1) sulfonamides with long-lasting action; (2) antibiotic associations and resistant staphylococci; (3) antimitotics and medullar grafts. The most eminent American, Russian and European specialists will take part in this meeting. For further information write Dr. P. Rentchnick, Case Stand 471, Geneva, Switzerland.

## 9TH MIDDLE EAST MEDICAL ASSEMBLY

Dr. Calvin H. Plimpton, F.A.C.P., Professor of Medicine and Chairman of the Department at the American University of Beirut, Lebanon, is Chairman of the 9th Middle East Medical Assembly which will meet May 8-10, 1959, in Beirut, Lebanon. Interested American physicians are urged to attend. Among the speakers will be Sir George Pickering of Oxford, England, and Dr. John P. Merrill, F.A.C.P., of the Peter Bent Brigham Hospital, Boston, Mass.

## OREGON CANCER CONFERENCE

An Oregon Cancer Conference will be held July 16-17, 1959, in Portland under the joint sponsorship of the Oregon State Medical Society, the Oregon Division of the American Cancer Society, the University of Oregon Medical School, and the Oregon Academy of General Practice. The Conference is planned for midsummer as a special feature of the Oregon Centennial celebration.

Among the seven guest speakers for the Conference will be two Fellows of the College, Drs. Ralph Jones, Jr., Coral Gables, Fla., and Leslie M. Smith, El Paso,

Tex. In addition to their individual presentations, each guest speaker will participate in one or more panel discussions.

A copy of the complete program and hotel reservation forms may be obtained by writing to Roscoe K. Miller, Executive Secretary, Oregon State Medical Society, 1115 S. W. Taylor St., Portland 5, Ore.

## 42ND ANNUAL MEETING OF THE AMERICAN DIETETIC ASSOCIATION

The 42nd Annual Meeting of the American Dietetic Association will be held in Los Angeles, Calif., August 25-28, 1959. The meeting will bring to the membership the latest developments in the sciences of nutrition, diet therapy, food technology, food administration, and recent trends in education. For information write the American Dietetic Association, 620 N. Michigan Ave., Chicago 11, Ill.

## 2ND WORLD CONFERENCE ON MEDICAL EDUCATION

Dr. Louis H. Bauer, F.A.C.P., Secretary General of The World Medical Association, New York, N. Y., recently announced that the Association has made initial arrangements for providing its participants at the Second World Conference on Medical Education to be held in Chicago, Ill., Aug. 30–Sept. 4, 1959, and the 13th General Assembly of The World Medical Association at Montreal, Canada, September 7–12, 1959, with a special chartered transportation plan. Members of the national medical associations and their families are eligible to apply for reservations on the chartered flights.

In commenting upon the advantages of the chartered transportation plan, Dr. Bauer noted that the Conference dates fall during the peak season of tourist travel which might make it more difficult for the participants to obtain the regular commercial reservation they wish; that the plan offers an opportunity for initial friendships to be established prior to the convening of the Conference, and hence, a preliminary exchange of ideas which could prove productive to the meetings. Substantial financial savings will be made possible for the member associations, their delegates and participants at the meetings. Additional information may be obtained from The World Medical Association, 10 Columbus Circle, New York 19, N. Y.

## University of Chicago Creates Section on Nuclear Medicine

Dr. Lowell T. Coggeshall, F.A.C.P., Dean of the Division of Biological Sciences, University of Chicago, recently announced the creation of the new Section on Nuclear Medicine in The School of Medicine. Five hundred thousand dollars provided by the Rockefeller Foundation will support the Section, together with additional funds provided by the University. The section will explore the increase in radiation due to by-products of all present uses of nuclear energy; the genetic and physiologic consequences of increased exposure of man and domesticated animals to ionizing radiation; legislative controls for activities responsible for exposure to radiation; medico-legal problems of personal injury of personnel engaged in nuclear energy industry, and the psychological aspects in a society threatened by exposure to nuclear energy.

HISTORY OF THE MEDICAL DEPARTMENT, UNITED STATES ARMY, IN WORLD WAR II

The Historical Unit of the U. S. Army Medical Service is in the process of preparing for publication, a series of volumes entitled MEDICAL DEPARTMENT, UNITED STATES ARMY, which relates the medical history of World War II. At the present time, 11 of these volumes are available. Volumes I, III, and IV would be of interest to the internist since they deal with the following subjects: Hospitalization and Evacuation; Preventive Medicine and Environmental Hygiene, World War II, and Preventive Medicine, Personal Health Measures and Immunization in World War II. The other subjects of the eight volumes currently available deal with Dental Service and Surgery. For further information or purchase, write to Superintendent of Documents, Government Printing Office, Washington 25, D. C.

## AMERICAN COLLEGE OF RADIOLOGY TO PRODUCE RADIATION PROTECTION MOTION PICTURE FOR PHYSICIANS

A motion picture illustrating the medical aspects of radiation, including protective measures in diagnostic radiologic examinations, will be distributed soon by the American College of Radiology to the nation's physicians. Supervising production of the 16 mm., half-hour color film will be a special committee of the American College of Radiology under the Chairmanship of Dr. Wendell G. Scott, Professor of Clinical Radiology, Washington University School of Medicine, St. Louis, Mo. The motion picture has been financed through a Rockefeller Foundation grant and College funds. Premiere showing of the film will be June 9, 1959, at the meeting of the American Medical Association in Atlantic City, N. J. Following the premiere, prints will be released immediately for distribution among the medical profession for showings at scientific programs, medical conventions, medical society meetings, hospital medical staff meetings and hospital association conventions.

## DR. ROBERT L. STERN MEMORIAL SCHOLARSHIP FUND

A fund has been established at the University of California School of Medicine at Los Angeles in memory of Dr. Robert L. Stern, F.A.C.P., who died on December 17, 1958. Its purpose is to provide, from the income earned, financial assistance to promising, but needy, medical students. This fund will permit the realization of a project close to Dr. Stern's heart to provide a way to continue in the medical field his own dedicated and unselfish work on behalf of his fellow man. Those interested should send gifts to Mr. James M. Gerstley, 630 Shatto Place, Los Angeles 5, Calif. The University will acknowledge gifts to each donor and Dr. Stern's family will be advised of each contribution received.

## AMERICAN MEDICAL ASSOCIATION NAMES DIRECTOR OF NEW DIVISION OF SCIENTIFIC ACTIVITIES

Dr. Edward L. Turner, F.A.C.P., Chicago, Ill., was recently named Director of the new Division of Scientific Activities of the American Medical Association. The Division will include the Councils on Mental Health, Scientific Assembly, and Medical Education and Hospitals; the American Medical Education Foundation, and the Department of Therapy and Research. Dr. Turner, who was former Dean of the University of Washington School of Medicine, Seattle, Wash., has served as Secretary of the Council on Medical Education and Hospitals since 1953. Dr. Walter S. Wiggins, F.A.C.P., Chicago, Ill., former Associate Secretary of the Council on Medical Education and Hospitals will succeed Dr. Turner as Secretary of the Council on Medical Education and Hospitals.

## American Society for the Study of Arteriosclerosis Merges with American Heart Association

The American Society for the Study of Arteriosclerosis has merged with the American Heart Association, it was recently announced by Dr. Francis L. Chamberlain, President of the Association. The Society has become the Council on Arteriosclerosis of the American Heart Association. This brings to eight the number of Councils now active in the Heart Association's program. The other Councils cover such areas as clinical cardiology, cardiovascular surgery, circulation, high blood pressure, rheumatic fever and congenital heart disease, basic science, and community service and education.

A principal objective of the American Heart Association is to unify all major fields of heart and circulatory disease within the Association's framework. Although arteriosclerosis has always been a primary concern of the Heart Association, he said, it has not had a formal Council covering that area. The Heart Association supports intensive research in arteriosclerosis, which is responsible for most heart attacks and strokes and is by far the leading cause of death in the United States.

## CONGRESSMEN HEAR JOINT "REPORT TO NATION" ON TEN-YEAR PROGRESS IN CONTROL OF CARDIOVASCULAR DISEASES

A unique "Report to the Nation" summarizing the progress made during the last ten years against heart and blood vessel diseases was delivered in Washington, D. C., February 19, 1959, by the American Heart Association and the National Heart Institute. Presented at the request of Senator Lister Hill of Alabama and Representative John E. Fogarty of Rhode Island, Chairmen of Senate and House Appropriations Subcommittees respectively, the report featured an objective review of advances in the cardiovascular field by six eminent physicians and scientists. Among them were three Fellows and one Master of the College. The Fellows included Dr. Howard B. Sprague, Boston, Mass.; Drs. Irvine H. Page, Cleveland, Ohio, and Robert W. Wilkins, Boston, Mass. The Master was Dr. Paul Dudley White, Boston, Mass.

The report was given in the United States Department of Commerce Auditorium before members of both Houses of Congress, government officials, leading physicians and laymen. Through the coöperative efforts of the two agencies, scientific research in the cardiovascular field has been greatly expanded and effective programs of public and professional education and community services for heart patients have been established. The joint report highlighted the advances in diagnosis, treatment, prevention and rehabilitation stimulated by scientific research which is the primary objective of both organizations.

## Personal Notes

Dr. Kermit E. Osserman, F.A.C.P., New York, N. Y., served as Chairman of the 2nd International Symposium on Myasthenia Gravis which was held at Los Angeles, Calif., April 18–19, 1959. The symposium was sponsored by the Myasthenia Gravis Foundation, Inc., and the National Institute of Neurological Diseases and Blindness.

Dr. Irving Greenfield, F.A.C.P., Long Island, N. Y., has recently been promoted to the position of Attending Physician in the Division of Internal Medicine at the Meadowbrook Hospital, East Meadow, Long Island, N. Y.

On January 22, 1959, Dr. Maurice S. Segal, F.A.C.P., Boston, Mass., conducted a Grand Medical Rounds Conference at the Boston City Hospital with presentation of two cases, "Bronchiectasis with Bronchospasm" and "Sarcoidosis." On January 28, he spoke on the topic of "Chronic Bronchial Asthma" to the Harvard Medical School students, also at the Boston City Hospital, and in the evening, he addressed the Boston Chapter of the American Association of Inhalation Therapists at the Carney Hospital. His subject was "Aerosol Therapy." Dr. Segal spoke on "Oxygen Equipment and Oxygen Therapy" at the opening session of the Annual Sales Meeting of the National Cylinder Gas Division of the Chemetron Corporation, held in Chicago, Ill., February 1–2, and on February 16, he conducted a seminar for the third-year students at the Boston City Hospital. The subject was "Pneumoconiosis, Sarcoid and Diffuse Pulmonary Infiltration." On February 25, he attended the Fifth Annual Postgraduate Seminar held at the Huron Road Hospital in Cleveland, Ohio, as guest speaker and gave a talk on "Chronic Pulmonary Emphysema."

Drs. Arthur J. Vorwald, F.A.C.P., Detroit, Mich., and Oscar A. Sander, F.A.C.P., Milwaukee, Wis., were two of the 15 health experts from seven countries who discussed the problems of "Pneumoconiosis" in Johannesburg, South Africa, February 9–21, 1959. The meeting was sponsored by the Pneumoconiosis Research Unit of the South African Council for Scientific and Industrial Research.

Dr. Dwight L. Wilbur, F.A.C.P., President of the American College of Physicians, San Francisco, Calif., discussed the subject, "Functional Gastrointestinal Disease," and Dr. Felix Wroblewski, F.A.C.P., New York, N. Y., discussed the topic "Transaminase and Other Serum Enzyme Tests in Clinical Medicine," at the Roanoke Memorial Hospital Postgraduate Day Program held in that city, March 19, 1959.

Five Fellows of the College were among the guest speakers featured at the 28th Annual Spring Clinical Conference of the Dallas Southern Clinical Society held in Dallas, Tex., March 23–25, 1959. The Fellows and the subjects they discussed are as follows: Dr. Leo H. Bartemeier, Baltimore, Md., "The Therapy of Psychosomatic Disorders" and "The Psychological Significance of Excessive Fatigue"; Dr. Edward P. Cawley, Charlottesville, Va., "Systemic Fungous Infections" and "Skin Disorders Accompanying Medical Progress"; Dr. Jerome W. Conn, Ann Arbor, Mich., "Hypoglycemia" and "Oral Blood Sugar Lowering Compounds"; Dr. Samuel B. Nadler, New Orleans, La., "The Differential Diagnosis of Jaundice" and "The Techniques in the Diagnosis of Thyrotoxicosis," and Dr. William A. Sodeman, Philadelphia, Pa., "Amebiasis and the Liver" and "Some Diagnostic Problems in Occlusive Peripheral Vascular Disease."

Dr. F. William Sunderman, F.A.C.P., Director, Division of Metabolic Research, The Jefferson Medical College of Philadelphia, Pa., was a guest speaker, and Dr. C. Wesley Eisele, F.A.C.P., Associate Professor of Medicine and Director of Postgraduate Medical Education, University of Colorado School of Medicine, Denver, Colo., was Moderator of a Morning Session at a Postgraduate Course in Medical Technology sponsored by the University of Colorado School of Medicine and the Colorado State Society of Medical Technologists held in Denver, Colo., March 16–20, 1959.

Dr. Norman M. Wall, F.A.C.P., Pottsville, Pa., Chairman of the Research Committee of the Pennsylvania Heart Association recently announced the availability of funds of the Association to support research in the field of heart disease.

Dr. William A. Steiger, F.A.C.P., Associate Professor of Medicine, Temple University School of Medicine, Philadelphia, Pa., was Moderator of a symposium on "Health Problems and Social Delinquency" which was sponsored by the Section of Public Health, Preventive and Industrial Medicine of the College of Physicians of Philadelphia, and held in Philadelphia, February 17, 1959.

Four Fellows of the College were speakers at the 1959 Atlanta Graduate Medical Assembly held February 16-18, 1959. The Fellows and their specialties were: Dr. Stewart G. Wolf, Jr., Oklahoma City, Okla., Internal Medicine; Dr. Edward H. Rynearson, Rochester, Minn., Endocrinology; Dr. William G. Sauer, Rochester, Minn., Gastroenterology, and Dr. William Dameshek, Boston, Mass., Heniatology.

Dr. I. Leonard Bernstein, (Associate), Cincinnati, Ohio, was elected to Fellowship in the American Academy of Allergy at the recent meeting of the Academy in Chicago. He presented a paper entitled, "Pulmonary Function in Normal and Asthmatic Children." Dr. Bernstein also was recently appointed Regional Consultant to the Jewish National Home for Asthmatic Children at Denver.

Dr. Isaac H. Richter, F.A.C.P., Brooklyn, N. Y., was recently appointed Attending Physician, Peripheral Vascular Diseases, at the Brooklyn Hebrew Home and Hospital for the Aged and Attending Visiting Physician, Peripheral Vascular Diseases, Coney Island Hospital.

Dr. Harry E. Banghart, F.A.C.P., Chief of Service B and Chief of the Arthritis Clinic at the Germantown Hospital, Philadelphia, Pa., discussed the subject, "Osteoporosis," at the joint meeting of the Academy of Medicine of New Jersey and the New Jersey Rheumatism Association at Newark, N. J., on February 19, 1959.

Dr. Fred E. Manulis, F.A.C.P., Palm Beach, Fla., was recently named Governor of the American College of Gastroenterology.

Four members of the College were among the out-of-state speakers at the 11th Annual Institute in Psychiatry and Neurology held at the Veterans Administration Hospital, North Little Rock, Ark., February 26–27, 1959. The three Fellows were Dr. Kenneth E. Appel, Ardmore, Pa.; Dr. Leo H. Bartemeier, Baltimore, Md., and Dr. Stewart G. Wolf, Jr., Oklahoma City, Okla. Dr. Bernard I. Kahn, San Francisco, Calif., was the Associate Member.

Dr. Albert J. Finestone, (Associate), Assistant Professor of Medicine at the Temple University Medical Center, Philadelphia, Pa., has been appointed Medical Consultant to the Skin and Cancer Hospital of Philadelphia which recently became a unit of the Department of Dermatology of the Temple University Medical Center.

Five Fellows of the College serve on the Scientific Advisory Board to the Tobacco Industry Research Committee. Included are: Drs. Kenneth Merrill Lynch, Charleston, S. C.; Richard J. Bing, St. Louis, Mo.; Julius H. Comroe, Jr., San Francisco, Calif.; Leon O. Jacobson, Chicago, Ill., and Stanley P. Reimann, Philadelphia, Pa.

Dr. James A. Brussel, F.A.C.P., Assistant Commissioner, New York State Department of Mental Hygiene, New York, N. Y., will have his novel, JUST MURDER, DARLING, published by Charles Scribner's Sons in July. He is also completing PSYCHIATRY FOR THE LAYMAN for Barnes and Noble. This volume will be available in October. The book not only explains the "normal," "subnormal," and "abnormal" of the human mind, but includes such other topics as love, religion, psychiatry, and the problems of the widow.

Dr. John J. Hammond, (Associate), St. Louis, Mo., was recently elected President of the St. Louis Heart Association at its annual meeting.

Drs. William McNeal Nicholson, F.A.C.P., Professor of Medicine and Director of Postgraduate Education, and Julian M. Ruffin, F.A.C.P., Professor of Medicine, both of the Duke University School of Medicine, Durham, N. C., were members of the faculty of the 4th Postgraduate Medical Seminar Cruise sponsored by the School of Medicine, April 2–14, 1959. The ports of visit included Nassau, Port-au-Prince, Kingston, and Cap-Haitien.

Two Fellows and an Associate of the College participated in the 23rd Annual Postgraduate Institute sponsored by the Philadelphia County Medical Society, Philadelphia, Pa., March 17–20, 1959. The members were Dr. Julian M. Ruffin, F.A.C.P., Durham, N. C., who discussed the subject, "Management of Idiopathic Steatorrhea"; Dr. Perry J. Culver, (Associate), Boston, Mass., who spoke on "Mechanisms of Malabsorption Syndromes," and Dr. Charles Wilmer Wirts, F.A.C.P., Philadelphia, Pa., who was Director of the Institute.

Dr. Chester M. Jones, M.A.C.P., Professor of Medicine, Emeritus, Harvard Medical School, Boston, Mass., served as Physician-in-Chief Pro Tempore at the Rhode Island Hospital, Providence, R. I., February 16-18, 1959.

Dr. Paul D. Camp, Jr., F.A.C.P., Richmond, Va., was recently selected as a Representative of the Virginia Heart Association on the National Board of Directors of the American Heart Association.

Dr. Jay C. Crager, F.A.C.P., Beaumont, Tex., a Past President of the Texas Heart Association, is Chairman of the Publicity and Public Relations Committee of the Texas Heart Association, and was recently elected President of the Jefferson County, Texas Tuberculosis Hospital Board of Managers.

Two Fellows of the College participated in the West Virginia Diabetes Association Meeting held in Charleston, W. Va., February 20-22, 1959. Dr. Thomas

H. McGavack, Martinsburg, W. Va., discussed the subject, "New Trends in Diabetes," and Dr. Garfield G. Duncan, Philadelphia, Pa., was a guest speaker at the Postgraduate Week-End Program.

Dr. Michael Bernreiter, F.A.C.P., Kansas City, Mo., presented a symposium on "Fundamental Electrocardiography," at a recent meeting of the Academy of General Practice.

Dr. Edgar S. Gordon, F.A.C.P., Madison, Wis., was elected President, and Dr. Austin S. Weisberger, F.A.C.P., Cleveland, Ohio, was named Secretary-Treasurer, at a recent meeting of the Central Society for Clinical Research.

Dr. John E. Kirk, F.A.C.P., St. Louis, Mo., was elected Treasurer at a recent meeting of the Gerontological Society.

Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala., was named First Vice President of the Southern Medical Association, at a recent meeting of the Association.

Dr. Anthony C. Cipollaro, F.A.C.P., New York, N. Y., was recently elected President of the American Academy of Dermatology and Syphilology.

Dr. Charles W. Dunn, F.A.C.P., Philadelphia, Pa., has closed his Philadelphia office and removed to Collegeville, Pa., where he continues to conduct a restricted practice in endocrinology. He is Visiting Endocrinologist to the State Hospital, Governor Bacon Health Center, and the Mental Hygiene Clinic of this institution at Farnhurst, Delaware. He is also associated with the Hospital for Mentally Retarded at Stockley, Delaware. Dr. Dunn is one of the earliest specialists in the field of endocrinology and was formerly actively engaged in a teaching capacity with several Philadelphia institutions. In the future, he will spend the winter months in Tobago, an island in the Caribbean near Trinidad. There he plans to engage in a program of study of mental health and mental retardation.

## **OBITUARIES**

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

- Dr. James Michael Bowers, F.A.C.P., Seattle, Wash., February 9, 1959
- Dr. Jay Bailey Carter, F.A.C.P., Evanston, Ill., December 6, 1958
- Dr. Herbert Eichert, F.A.C.P., Miami, Fla., February, 1959 (exact date un-known)
- Dr. James Christopher Gillie, (Associate), Fort William, Ontario, Can., January 7, 1959
- Dr. Lester Hollander, F.A.C.P., Pittsburgh, Pa., February 2, 1959
- Dr. Hertel Philip Makel, Sr., F.A.C.P., Moorestown, N. J., November 7, 1958

## DR. CHARLES D. AMBROSE

Dr. Charles D. Ambrose, (Associate), died in Ligonier, Pennsylvania, on March 15, 1958. Heart failure was listed as the cause of his death. Dr. Ambrose was born in 1876 and attended the University of Pittsburgh School of Medicine, from whence he was graduated with a degree of M.D. in 1900. He restricted his practice to the City of Latrobe, Pennsylvania, and he was on the staff of the Latrobe Hospital throughout his 51 years of practice. Dr. Ambrose was a member of the American College of Physicians (Associate). He was also a member of the American Medical Association and of his state and county societies. He served the latter, namely the Westmoreland County Society, as Secretary.

Dr. Ambrose is survived by his widow, Mrs. May Y. Ambrose of Ligonier, Pennsylvania.

FRANK J. GREGG, M.D., F.A.C.P., Governor for Western Pennsylvania

## DR. ROBERT CHOBOT

Dr. Robert Chobot, F.A.C.P., was born March 22, 1901, New York, New York, and died on September 26, 1958, in London, England, of coronary thrombosis with myocardial infarction.

Dr. Chobot received his Bachelor of Arts degree at Columbia University, in 1921, and Doctor of Medicine degree at Columbia University College of Physicians and Surgeons in 1924. He received his postgraduate training in pathology at the Presbyterian Hospital 1924–26, and in applied immunology at the New York Hospital and Cornell University Medical College in 1926.

His appointments were as follows: Associate Clinical Professor of Pediatrics, New York University Post-Graduate Medical School, since 1929; Chief of Children's Allergy Clinic, University Hospital, since 1928; Attending Physician, Allergy Institute, Roosevelt Hospital, since 1926 and Consulting Immunologist, Beekman-Downtown Hospital, since 1942.

Dr. Chobot was a member of the following organizations: American Academy of Allergy (President 1943-44); New York Association of Allergy Clinics (Secretary 1939-58); Society for the Study of Asthma and Allied Conditions (Past President); American Medical Association; Pan-American Medical Society; Alpha Omega Alpha. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians since 1931.

He was the author of a book on "Pediatric Allergy" which was published in 1951. Also, many of his articles were published in the leading national and state medical journals.

Dr. Chobot is survived by his widow, Mrs. Alice Chobot, 880 Fifth Avenue, New York, New York, His confreres note with sincere regret the passing of Dr. Chobot. IRVING S. WRIGHT. M.D., F.A.C.P.,

Governor, Eastern New York State

## DR. BEAUMONT SANFIELD CORNELL

Dr. Beaumont Sanfield Cornell, Fellow and Life Member of the American College of Physicians, died September 16, 1958, of coronary occlusion. Dr. Cornell was born March 27, 1892, in Athens, Ontario, Canada. He received his M.D. from the University of Toronto Faculty of Medicine in 1916, and served as an intern in 1917 at St. Vincents Hospital in Brockville, Ontario, Canada. He continued his medical education serving as a Fellow at the University of Toronto Faculty of Medicine and as a Research Fellow in the Department of Medical Research.

Dr. Cornell had been a Member of the Staff and Lecturer for the Nurses at the Lutheran Hospital since 1928 and Consulting Physician for the Fort Wayne State

School for the mentally deficient since 1930.

He was a member of the American Diabetes Association, the American Gastroenterological Association, the American Medical Association, the Fort Wayne Medical Society and of Alpha Omega Alpha. Dr. Cornell was a Diplomate of the American Board of Internal Medicine.

He was active in the civic theater and wrote several plays. He also achieved prominence through his landscape painting. He was a member of the Scottish Rite

and of the Fortnightly Club.

Dr. Cornell was Founder and Editor of the American Journal of Digestive Diseases which became the official journal of the Gastroenterological Association.

He is survived by his wife, Myrtle, who may be addressed at The Oaks, Rural

Route 2, Huntington, Indiana.

KENNETH G. KOHLSTAEDT, M.D., F.A.C.P., Governor for Indiana

## DR. EDGAR FRANCIS COSGROVE

Dr. Edgar Francis Cosgrove died September 3, 1958, at Pittsburgh, Pennsylvania, of carcinoma of the stomach. He was born at Munhall, Pennsylvania on August 30, 1909. He received his college and medical education at the University

of Pittsburgh and was granted his M.D. degree in 1936.

After interning at the Saint Francis Hospital (Pittsburgh), Dr. Cosgrove commenced his graduate training at the Saint Francis Hospital and completed his residency after the termination of World War II from 1946-1948. Thereafter, he became associated with the University of Pittsburgh School of Medicine, where he ultimately achieved the title of Assistant Clinical Professor of Medicine. He had also served as Chairman of the Committee on Graduate Education of the School of Medicine since 1948.

Dr. Cosgrove was an Active Staff Member of the Presbyterian, Veterans Administration, Saint Francis and Saint Margaret Memorial and Municipal Hospitals of this city and was Consultant Cardiologist at the Homestead Hospital.

He served in the Medical Corps A.U.S. during World War II and was dis-

charged with the rank of Lieutenant Colonel.

Dr. Cosgrove was a member of the American Medical Association and the State and County societies. He was a Diplomate of the American Board of Internal Medicine and a Fellow in the American College of Physicians since 1953.

He is survived by his wife, Mrs. Sarah Lee Cosgrove of Pittsburgh and two children, Charles William and Katherine Richeson Cosgrove.

Frank J. Gregg, M.D., F.A.C.P., Governor for Western Pennsylvania

## DR. GEORGE WILLIAM CUMBLER

Dr. George W. Cumbler, F.A.C.P., was born October 8, 1893, at Steelton, Pennsylvania, and died on November 14, 1958, in New York, New York, of coronary atherosclerosis.

Dr. Cumbler received his Bachelor of Science degree at Princeton University, New Jersey, 1915, and his degree of Doctor of Medicine at the New York University College of Medicine in 1920. He interned at Bellevue Hospital, New York City, 1920–21.

His appointments were as follows: Faculty Member, Columbia University College of Physicians and Surgeons, 1921–35; Attending Physician, Grasslands (Valhalla) since 1943; St. Agnes (White Plains) Hospital since 1945; Chief of Arthritis Clinic, White Plains Hospital since 1943 and Visiting Physician, New York City Correction Hospitals since 1935.

Dr. Cumbler was a member of the following organizations: American Medical Association; Medical Society of the State of New York; New York County Medical Society; New York Academy of Medicine; American Rheumatism Association and New York Rheumatism Association. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians, 1931, and a Life Member since 1934.

Dr. Cumbler is survived by a son, John T. Cumbler, Titusville, New Jersey. It is with sincere regret his loss is recorded.

IRVING S. WRIGHT, M.D., F.A.C.P., Governor, Eastern New York State

## DR. EUGENE FLOYD DUBOIS

One of America's most distinguished physicians and scientists, Dr. Eugene Floyd DuBois died on February 12, 1959, in New York City, at the age of 76 of cerebral and coronary arteriosclerosis with an acute myocardial infarction.

Dr. DuBois was born on June 4, 1882, at West Brighton, Staten Island, New York. He received his Bachelor of Arts degree from Harvard University in 1903 and his degree of Doctor of Medicine from Columbia University College of Physicians and Surgeons in 1906. In 1948 he was awarded an honorary degree of Doctor of Science at Rochester University.

After internship at Presbyterian Hospital, 1907–1908, where he acted as Assistant Pathologist, he went to Germany to study Metabolism. Dr. Graham Lusk met him in Berlin, and Dr. DuBois returned to the United States and became Medical Director of the Russel Sage Institute of Pathology of which Dr. Lusk was Scientific Director. Under Dr. DuBois's guidance, Russel Sage Institute has had world-wide influence in advanced scientific knowledge in the field of Metabolism and from his "Calorimeter Room" have gone forth many leading medical scientists and educators.

Dr. DuBois was Director of the Second Medical (Cornell) Division, Bellevue Hospital, 1919-'32. He was Professor of Medicine at Cornell University Medical College from 1930-1941; Physician-in-Chief at the New York Hospital from 1932-'41 and Professor of Physiology at Cornell from 1941-'50 when he became Emeritus Professor. He was an outstanding authority in the fields of submarine warfare and aviation medicine for which he received the Navy Cross and the Commendation

and Ribbon Bar. He retired from the Navy after World War II with the rank of Captain.

Dr. DuBois belonged to many societies, including: The National Academy of Science; Philosophical Society; American Physiological Society; The Aeromedical Association; Society of Experimental Biology and Medicine; Association of American Physicians; Harvey Society and the Institute of Nutrition. He served as President of the American Society for Clinical Investigation and as Trustee of the Marine Biological Laboratory in Woods Hole, Massachusetts. He had been a Fellow of the American College of Physicians since 1937.

Among the many honors which he received was the Kober Medal of the Association of American Physicians in 1947 and the Academy Medal of the New York Academy of Medicine in 1956. He had been nominated to receive the John Phillips Memorial Award of the American College of Physicians in April 1959.

While the accomplishments and honors of Dr. DuBois were many, his influence on his students and associates by reason of his personality and character, was even more extraordinary. Dr. David Barr, his life-long friend and successor, has stated: "This extraordinary influence has been attributable only in part to his mastery of experimental procedure and the intrinsic value of his scientific contributions. Its essence derives from his own character and personality. Inspiration has come to others from his abiding faith in principles of scientific and personal conduct, from his integrity and tolerance and from his sympathetic understanding of the problems of those about him. His character has influenced behavior of his colleagues. It has also influenced innumerable students who have learned from him lessons of critical evaluation, clear expression, unvarying courtesy and true humility."

In an article entitled "The Clinical Clerkship in Medicine," published in the Journal of the American Medical Association, August 21, 1956, Dr. DuBois stated as follows: "The purpose of instruction is to teach the students to teach themselves; the manner of instruction is by example and work; the spirit of instruction is sympathy for, and faith in, the students."

Dr. DuBois's life may be summarized by the citation of the New York Academy of Medicine as: "Eugene Floyd DuBois, physiologist, physician, educator, patriot."

Dr. DuBois is survived by his widow, Mrs. Rebeckah DuBois, 200 East End Avenue, New York City, and three children. They are: Eugene DuBois, New York City; Mrs. Rebeckah Glazebrook, New York City, and Dr. Arthur DuBois, Philadelphia, Pennsylvania. It is with deep regret and a great sense of profound appreciation that his thousands of students and confreres pay homage to this beloved, scholarly and gentle man.

IRVING S. WRIGHT, M.D., F.A.C.P., Governor, Eastern New York State

## DR. MILTON EDWARD HUBBARD

On Christmas Eve, 1958, Dr. Milton Edward Hubbard, Associate, died of coronary thrombosis. A Mormon, he was born in Willard, Utah, on October 18, 1892. He received his M.D. degree from the University of Illinois College of Medicine, in 1928, followed by an internship in Los Angeles, California.

From then on he was associated with the Veterans Administration for a period of career service extending over 20 years. From 1929 to 1948 he was Chief Medical Officer, Veterans Administration Hospital, Los Angeles, California. From 1949 to 1950 he was Director of Professional Services, Veterans Administration Hospital, Oakland, California. He was forced to retire because of ill health.

During the war years, 1942 to 1946, he was a Colonel (MC), A.U.S. During this time, he was a frequent contributor to the medical literature. He became an

Associate of the American College of Physicians in 1945 at the age of 53. His physical disabilities prevented him from satisfying the basic requirements for advancement to Fellowship status.

He was a member of: the American Medical Association; the Association of Military Surgeons of Southern California (Past President); the Los Angeles County Medical Association; the Hollywood Academy of Medicine, and the California Medical Association.

To his wife, Mrs. Hope F. Hubbard, 255 Buckingham Way, Apartment 604, San Francisco 27, California, the College extends its deepest sympathy.

MAURICE Z. COOPER, M.D., Associate, Acting Director, Medical Service, Veterans Administration Central Office.

## DR. DANIEL JOSEPH McCARTHY

On October 9, 1958, Dr. Daniel Joseph McCarthy, F.A.C.P., died following an unusually productive professional life.

He had resided in Philadelphia, save for absences occasioned by professional missions. Born in 1874, he attended the University of Pennsylvania, from which he graduated in medicine in 1895. His varied appointments indicate the scope of his influence. These included the following: Emeritus Professor of Medical Jurisprudence, University of Pennsylvania School of Medicine; Former Co-Founder and Director, McCarthy-Kirby Foundation, University of Pennsylvania School of Medicine; Former Director of Sociological Research, Municipal Court of Philadelphia; Trustee, Drexel Institute; Founder and Director, The McCarthy Research Foundation, Temple University; Consulting Neurologist, Norristown State Hospital; Member

of Council, Veterans Administration, Washington, District of Columbia.

During 1914, he served as Liaison Officer in the American Ambulance Corps in France. The following year he served in the Diplomatic Service as Special Assistant to the Ambassador to Germany. Attached to the State Department, he was given an assignment in Russia in 1916. While serving with the Headquarters of the A.E.F., 1917-1918, he attained the rank of Lieutenant Colonel.

His membership in various organizations was as follows: American Medical Association; American Neurological Association (President, 1933); Philadelphia Neurological Association (President, 1934); American Neurological Society; American Psychiatric Association; Association for the Study of Internal Secretions; Association for Research in Nervous and Mental Diseases; Philadelphia County Medical Society; Philadelphia Psychiatric Society; Medical Club of Philadelphia; College of Physicians of Philadelphia; John Morgan Society of Philadelphia. He became a Fellow of the American College of Physicians in 1923.

His publications included many contributions to journals and books entitled, PRISONER OF WAR IN GERMANY and INSANITY AND THE LAW.

His many friends in the College join in expressing admiration for Dr. McCarthy, and extend sympathy to his wife, Mrs. Elizabeth White McCarthy, 107 Suffolk Avenue, Ventnor City, New Jersey, and son, Daniel J. McCarthy, Palm Beach, Florida.

WILLIAM A. JEFFERS, M.D., F.A.C.P., Governor for Eastern Pennsylvania

## DR. ORMAN CLARENCE PERKINS

Dr. Orman Clarence Perkins, F.A.C.P., was born on April 23, 1892, in Newbourg, Maine, and died on August 18, 1958, at Crawford Notch, New Hampshire, of a myocardial infarction.

Dr. Perkins received his A.B. degree at Bates College, Lewiston, Maine, 1915; M.A. degree at Columbia University, 1917, and M.D. degree at Long Island College Hospital in 1921. He received his postgraduate training in neurology at the National Hospital for Paralyzed and Epileptics, London, England, 1926.

His appointments were as follows: Faculty Member, Long Island College of Medicine (later State University of New York College of Medicine in New York City) from 1916–1953 (Professor of Neurology since 1927); Attending Neuropsychiatrist, Long Island College, Bushwick, Caledonian, Brooklyn State, Creedmore State (Queens Village), Central Islip State, Kingston Avenue and Swedish Hospitals and Norwegian Lutheran Deaconesses' Home and Hospital; Consulting Neuropsychiatrist, Victory Memorial, Bethany Deaconess, Evangelical Deaconess, Methodist Deaconess, Brooklyn, Jamaica, Kings County and Veterans Administration Hospitals.

Military Service: Commander, (MC), U.S. Navy Reserve, 1943-45.

Dr. Perkins was a member of the following: American Medical Association; American Anatomical Association; American Academy of Compensation Medicine; Medical Society of the State of New York; New York Neurological Society; New York Academy of Medicine; Kings County Medical Society; Associated Physicians of Long Island; Brooklyn Neurological Society (Past President); Brooklyn Pathological Society (Past President); Brooklyn Psychiatric Society and a Fellow of the American College of Physicians since 1928.

Many of Dr. Perkins' articles appeared in leading state and national medical journals.

He is survived by his wife, Mrs. Margaret S. Perkins, 829 Carroll Street, Brooklyn 15, New York. His confreres note with sincere regret the passing of Dr. Perkins.

IRVING S. WRIGHT, M.D., F.A.C.P., Governor, Eastern New York State

## DR. HERMAN HARLAN RIECKER

Dr. Herman Harlan Riecker, F.A.C.P., died after a brief illness in St. Joseph Mercy Hospital, Ann Arbor, Michigan, on January 5, 1959. His death came as a shock to his friends and patients, and as an unexpected tragedy and a bitter loss to his professional colleagues; not only to those on the staff of St. Joseph Mercy Hospital, but to the medical profession in Michigan and the nation. His many and varied activities made him widely known and earned for him a position of respect for his character and for his solid achievements and leadership. He lived, practiced and taught in one of the most fruitful and productive periods in the evolution of medicine, and took an active and constructive part in most phases of its development.

Dr. Rieker was born March 28, 1895, in Pennsville, Ohio, a son of Ernest J. and Allie Zumbro Riecker. Shortly after Dr. Riecker's birth the family moved to Beverly, Ohio, where he attended grade and high school. Upon graduation from the latter, he next attended nearby Marietta College where he made an outstanding record, not only in scholarship, but also in intra-mural activities; serving as editor of the college newspaper and also continuing his ardent interest in outdoor sports by being captain of the football team for two years. Graduating from the college with an A.B. degree in 1917, he immediately joined the Army, serving two active years until his honorable discharge in 1919.

His interest in medicine probably was stimulated by an association with several brilliant young medical officers with whom he served, and his choice of The Johns Hopkins University School of Medicine was certainly influenced by the fact that his boyhood friend and neighbor, Frank Adair, had recently graduated from that school.

During his student days in medicine, he interned for one summer at the Peter Bent Brigham Hospital in Boston. Graduating from The Johns Hopkins University School of Medicine, in 1923, he was appointed an interne to the New York Hospital where he served from July, 1923 to July, 1925. The following year he was Resident Physician at the Barnes Hospital in St. Louis. In 1926 he was offered and accepted the post of Instructor in Medicine at the University of Michigan Medical School. This was indeed an eventful and happy year in his life for on September 2, he married Elizabeth Wertz Day of Millersburg, Pennsylvania, whom he had met in Baltimore while he was attending medical school and she was a student at Goucher College.

He was soon advanced to Assistant Professor and in 1935, became Associate Professor of Internal Medicine. He was a stimulating, provocative and highly effective teacher to undergraduates and graduates alike. Widely and wisely read, he was a master of medical literature in several languages. His inquiring mind, however, accepted nothing without a solid background of proof.

In the early "'30s" graduate education was receiving a good deal of attention, but postgraduate education was at a low ebb or nonexistent. Dr. Riecker became more and more interested in its problems and needs. He played an important part in the organization of postgraduate teaching as a function of medical schools in coöperation with the State Medical Society. From these efforts developed one of the outstanding postgraduate teaching programs in the country. Its superb operation to this day is a concrete testimony to his success.

Dr. Riecker resigned from the Department of Medicine of the University in 1941 to enter private practice as an active member of the Department of Internal Medicine at St. Joseph Mercy Hospital. However, he continued active in the Department of Postgraduate Medicine in the University until 1947. No matter where, or in what capacity he labored, he was always the inquiring and stimulating teacher up until the very end.

Another of his abiding interests was in rheumatic fever control. He felt with others that many cases of this disease went unrecognized until irremediable harm had been done. Dr. Rieker led in the establishment in 1944 of the Rheumatic Fever Control Committee of the Michigan State Medical Society. He later became Chairman of the Committee. The worth of its performance is well known.

Dr. Riecker was the author of numerous articles on medical topics varying in subject from medical education to hematology, cardiology, rheumatic fever and the philosophical. He was Editor of the Health and Hygiene column of the Detroit News for several years. He wrote with ease, clarity and simplicity. He was an active contributing member of many organizations. He belonged to the Alpha Tau Omega Fraternity, the Phi Chi Fraternity and the Sigma Xi honorary fraternity. He was a very active member and Past President of the Washtenaw County Medical Society. He was a Diplomate of the American Board of Internal Medicine and held membership in the Michigan State Medical Society, American Medical Association, American College of Physicians, Michigan Heart Association, The Central Society for Clinical Research and was an Emeritus Member of the American Society for Clinical Investigation.

Dr. Riecker was a great physician in the truly Hippocratic sense, in that he was devoted to his patients. He taught his art and science unceasingly and he was thoroughly honest with himself and with the rest of the world. He had a delightful sense of humor that gave him a quiet smile rather than a hearty laugh from the day to day whimsical events of living. If one must be said to have a hobby, it was his home. There he could read, study, enjoy friends, music and take pride with his wife in the growth, education and development of their three sons, a source of tremendous satisfaction and of paramount interest to both of them.

Dr. Riecker is survived by his wife Elizabeth, and their three sons: John, who practices law in Midland, Michigan; James, who is in industrial relations with the Kaiser Aluminum Company in Erie, Pennsylvania, and Frederick, a senior at University High School. He is also survived by two grandsons, John and Stephen; his father age 88 years; and two younger brothers, Hubert and Leland of Beverly, Ohio.

Dr. Riecker will never be forgotten by them or by us, but perhaps as important he will always be remembered by a generation of medical students who, having been for a time his disciples, will apply his precepts to the problems of disease as they confront them in time to come. This would indeed please him.

FREDERICK A. COLLER, M.D., Ann Arbor, Michigan

## DR. EDWARD ADAM STRECKER

Dr. Edward Adam Strecker, F.A.C.P., died in the Jefferson Hospital, Philadelphia, Pennsylvania, January 5, 1959, at the age of 72.

He was born and educated in Philadelphia, attending LaSalle College and The Jefferson Medical College of Philadelphia where he received his M.D. degree in 1911. His professional appointments included: Emeritus Professor of Psychiatry, University of Pennsylvania School of Medicine, and the University of Pennsylvania Graduate School of Medicine; Consultant to the Surgeons General of the United States Army and Navy; Senior Consultant, Veterans Administration Hospital, Philadelphia; Consultant and Chief of Service, Institute of the Pennsylvania Hospital, and Psychiatrist, Pennsylvania Hospital, Philadelphia. During the years 1926 to 1932 he served as Clinical Professor of Psychiatry and Mental Diseases at Yale University School of Medicine.

He was a member of: the American Medical Association; the American Neurological Society; the Association for Research on Nervous and Mental Diseases; the American Psychiatric Association; the College of Physicians of Philadelphia; The Philadelphia Neurological Society, and the Medical Society of the State of Pennsylvania. He was a Diplomate of the American Board of Psychiatry and Neurology and became a Fellow of the American College of Physicians in 1930.

Dr. Strecker was the author of more than 200 published papers and several books. His were among the most potent hands guiding the development of psychiatry in this country. He combined the happy faculty of being an inspiring teacher, and of having the vision to work effectively with various groups, in medicine, law, and government, toward the constructive application of psychiatric principles. During World War I, he served as a Neuropsychiatrist with the 28th Division, seeing active duty for two years in France.

To his wife, Elizabeth W. Strecker, his colleagues offer sympathy and understanding. Edward Strecker was indeed an unusually wise and compassionate physician.

WILLIAM A. JEFFERS, M.D., F.A.C.P., Governor for Eastern Pennsylvania

## DR. GEORGE H. WILSON

Dr. George H. Wilson, F.A.C.P., respected and beloved internist of Lexington, Kentucky, died, as he would have wished, at work on September 26, 1958. He suffered a severe myocardial infarction in 1942 but returned to his practice and retained an active interest in all things medical until a recurrence of myocardial infarction caused his death.

Dr. Wilson was born in Lexington in 1884. He was graduated first from the University of Kentucky, then received his M.D. degree from the University of Michigan Medical School, in 1910. His postgraduate training was in the University of Michigan Hospital, The New York Post-Graduate Hospital, New York City Hospital and the Hudson Street Hospital of New York. He entered practice in Lexington in 1913, and in addition to his private practice he was for many years Medical Director of the Lexington City School System. He was a member of the Staff of St. Joseph,

Good Samaritan and Central Baptist Hospitals.

Dr. Wilson became a Fellow of the American College of Physicians in 1927 and was a Diplomate of the American Board of Internal Medicine. He was a member of the local and state medical societies, the American Medical Association, and the Southern Medical Association. In 1926 he was President of the Fayette County Medical Society. During World War I, he was attached to Base Hospital No. 40, and was discharged with rank of Captain. He was active in alumni affairs of the University of Kentucky, was a member of the Executive Board of the Alumni Association and served two terms as President of the Alumni Association. He also served at one time as a Trustee of the University of Kentucky. He was a member of the Second Presbyterian Church and the Lexington Rotary Club.

Dr. George Wilson is fondly remembered by the internists of Lexington because of his keen interest in medicine and because of the help and encouragement he so freely extended to younger internists. He was respected for his high idealism. He was admired for the courage which carried him on for sixteen years with serious

cardiac disability. He is missed by all of us.

CARL H. FORTUNE, M.D., F.A.C.P., Lexington, Kentucky

## DR. LEE ROY WOODWARD

Dr. Lee Roy Woodward, F.A.C.P., of Mason City, Iowa, died of coronary occlusion on December 9, 1958. He was born in Mason City on September 18, 1885. He received his B.S. degree from Grinnell College, Grinnell, Iowa, in 1909, where he was elected to Phi Beta Kappa. His medical degree was obtained from Rush Medical College in 1917. Following postgraduate training, he practiced Internal Medicine in the town of his birth. He was a Staff Physician of the Park Hospital.

Dr. Woodward was a kindly physician, beloved by his patients and respected by his colleagues. He was active in the affairs of organized medicine in the state and was a member of the Cerro Gordo County Medical Society, the American Medical Association and the Iowa State Medical Society of which he was President in 1943. He was also active in the affairs of the Iowa Clinical Medical Society and was President of this society in 1930. He was a member of the American Society of Clinical Pathology, and the Austin Flint Cedar Valley Medical Society (Secretary 1926-28). He became a Fellow of the American College of Physicians in 1931 and a Life Member in 1944. From 1941 to 1945 he was a member of the Medical Advisory Board for the Iowa Selective Service Commission.

Dr. Woodward was active in improving the standards of medical care and medical practice both in his local community and throughout the state, and his efforts in this behalf have left a lasting impression. His community and the medical profession of the state have lost a devoted practitioner of Internal Medicine. The College of Physicians extends its sincere sympathy to his surviving son, Dr. E. R. Woodward, University of California School of Medicine at Los Angeles, Los Angeles

24, California.

WILLIS M. FOWLER, M.D., F.A.C.P., Governor for Iowa

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References: 1. Cooperative Study of 4092 patients by 105 physicians, Department of Medical Research, Winthrop Laboratories.

2. Lichtman, A.L.: Kentucky Acad. Gen. Pract. J. 4:28, Oct., 1958.

\*tran'kwi-lak'sant [<L. tranquillus, quiet; L. laxare, to loosen, as the muscles]

Trancopal (brand of chlormezanone) and Caplets, trademarks reg. U.S. Pat. Oil.,

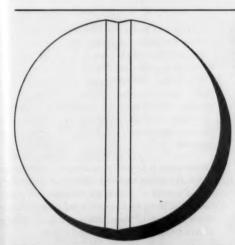
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# DOUBLE POTENCY

AT LOW COST TO YOUR PATIENT



# Pentids 400'

For the treatment of penicillin susceptible infectionsranging from mild to moderately severe-due to hemolytic streptococcus / pneumococcus / staphylococcus / and for the prevention of streptococcal infections where there is a history of rheumatic fever

Clinical effectiveness confirmed by millions of cases Specific in many common infections Daily dosage may be spaced without regard to mealtime Ease of administration with oral penicillin Economy for the patient

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Squibb Quality- the Priceless Ingredient

#### new convenient oral tablets

PENTIDS '400,' each scored tablet con-tains 400,000 units of penicillin G potas-sium buffered, bottles of 12 and 100.

PENTIDS, 200,000 units of buffered penicillin G potassium per scored tablet, bottles of 12, 100,

NTIDS FOR SYRUP, 200,000 units of penicillin G potassium per teaspoonful (5 cc.), 12 dose

PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 100, and

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin G potassium per tablet, vials of 12 and

PENTIDS-SULFAS TABLETS, 200,000 units of penicillin G potassium with 0.5 Gm. triple suites per tablet, bottles of 20, 100, and 500.

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### IS THIS YOUR PATIENT?



EARLY POSTMENOPAUSE

Complains of low back pain, vague aches and fatigue Posture is poor No x-ray evidence of bone lesions



LATER POSTMENOPAUSE

Back pain is severe, spreading to hips ("girdle pain") Patient is round shouldered, walks with a stoop X-ray reveals compression fractures of lower vertebrae 3.



70 AND OVER

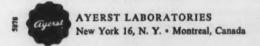
Fracture of hip after a minor fall X-ray reveals fracture of neck of former X-ray reveals compression fractures of lower lumbar vertebrae

These three patients have osteoporosis. Early diagnosis and treatment with "Formatrix" is important because osteoporosis is probably the only age change that can be averted. With "Formatrix" therapy, relief from the symptoms of low back pain, vague aches and fatigue may be obtained in as little as a few weeks. "Formatrix" supplies the essential materials to stimulate increased bone formation and prevent further loss of bone substance that leads eventually to loss of height, stooped posture, and disabling fractures.

The highest incidence of osteoporosis may be found among the 14,000,000 women in the U.S.A. who are 55 years of age and over. Some investigators claim that almost all women past the menopause will show some degree of osteoporosis; furthermore, if all these women were examined carefully, 50 per cent would show x-ray evidence of decreased bone mass.

Suspicion may be the handiest diagnostic tool since presenting symptoms vary from mild to severe and incapacitating pain, and no x-ray evidence of spinal degeneration is available until about 30 per cent of the bone matrix is lost. Between these two extremes there are other signs of estrogen deficiency such as wrinkted and thinning skin, a tendency to appear older than stated years; there may also be hypercalciuria when postmenopausal osteoporosis is complicated by acute osteoporosis of disuse.

Osteoporosis is primarily an atrophic condition of bone matrix formation and any factor that depresses osteoblastic activity or retards the formation of protein and connective tissue such as prolonged immobilization, contisone therapy, or malnutrition will favor development of osteoporosis in both male and female.





"FORMATRIX" contains three most essential bone building materials necessary for matrix formation, estrogen, androgen and vitamin C.

The estrogen component of "Formatrix" stimulates osteoblastic activity, thus aiding calcium and phosphorus deposition; it also imparts a feeling of "wellbeing." The anabolic action of methyltestosterone promotes the synthesis of protein and restores a positive nitrogen balance. Together, these hormones have a greater effect on bone and protein metabolism than either alone, and side effects are minimized because of the opposing action of the two steroids on sex-linked tissues. Vitamin C plays an important role in formation of intercellular cement substance and amino acid synthesis. "Formatrix" has a large amount of vitamin C to aid in new bone matrix formation and to further help in the healing of fractures.

#### "FORMATRIX" - each tablet contains:

Conjugated estrogens equine ("Premarin" •)	1.25	mg.
Methyltestosterone	10.0	mg.

Dosage: 1 tablet a day - In the female, three weeks of treatment with a rest period of one week between courses is recommended.

Supplied: Tablets, bottles of 60 and 500.

LITERATURE AVAILABLE ON REQUEST



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EARLY POSTMENOPAUSE

No x-ray evidence of bone lesion



LATER POSTMENOPAUSE

X-ray reveals compression fracture of lower vertebrae



70 AND OVER

X-ray reveals fracture of neck of femur

TO RELIEVE LOW BACK PAIN - TO PROMOTE HEALING OF FRACTURES

in osteoporosis

for matrix formation

(Brand of Steroid - Vitamin Combination)

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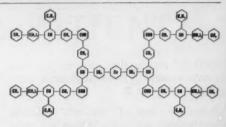
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# NEW THERAPEUTIC CHEMICAL IN

CONSTIPATION



Calcium Bis-(Dioctyl Sulfosuccinate)

The discovery by Wilson and Dickinson<sup>1</sup> at the University of Michigan that dioctyl sodium sulfosuccinate could correct constipation through fecal softening action marked a real advance in therapy. In cases of unimpaired bowel motility this new physico-chemical principle presented a new means of correcting bowel dysfunction without the need of catharsis.

Continuing research has now led to the development of a new therapeutic surfactant with more than double the surfactant effectiveness of the original dioctyl sodium sulfosuccinate.

This new substance, calcium bis-(dioctyl sulfosuccinate), reduces interfacial tension to a minimal value at a concentration of only 0.035 per cent. A minimal value of this order in dynes per centimeter requires 0.1 per cent or more of the older dioctyl sodium sulfosuccinate.

INTERFACIAL TENSION (Oil-Water Interface) Calcium Bis-(Dioglyl Sulfosuccinate)		
Dynes/cm.	Concentration	
55.0	0.00%	
13.3	0.01%	
9.9	0.02%	
8.4	0.03%	
7.4	0.035%	

Improved homogenization of the immiscible lipoid and aqueous phases of the intestinal content depends upon maximum reduction of interfacial tension. The greatest degree of fecal softening is achieved with surfactant agents capable of reducing interfacial tension to minimal values. Calcium bis-(dioctyl sulfosuccinate) represents a markedly more effective surfactant agent since maximum surfactancy results from less than half the concentration of previously used surfactants.

DOSAGE:

DOXICAL 240 mg. SOFT GELATIN CAPSULES – for adults, one daily.

DOXICAL 50 mg. SOFT GELATIN CAPSULES – for children and adults with minimum needs, one to three daily.

Wilson, J. L., and Dickinson,
 D. G.: J.A.M.A. 158:261-263
 (May 28) 1955.

This new chemical, definitely superior in surfactant action, is indicated in the treatment of chronic constipation where non-laxative fecal softening therapy is the preferred regimen.

The usual adult dose is 240 mg. daily. For children and adults with minimum needs, 50 to 150 mg. daily may be given.

DOXICAL

LLOYD BROTHERS, INC.

CINCINNATI 3, OHIO

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# UREVERT

(LYOPHILIZED UREA AND TRAVERT

# A SUPERIOR METHOD OF INTRACRANIAL DECOMPRESSION

Among the numerous intracranial problems in which Urevert has been shown to be highly beneficial, reduction of a pseudomeningocele is a striking demonstration of dramatic brain decompression.

Reduction of intracranial pressure with Urevert exposes many obscure areas and often permits surgical procedures to be carried out with minimum retraction and less damage to normal brain tissue. Urevert has been described as "far superior in every respect to all other agents commonly used for this purpose."\*

In depressed fractures or when intracranial pressure is acute, Urevert may be life-saving. Administered intravenously, Urevert exhibits only very occasional and relatively insignificant side effects.

\*Javid, M.: Urea — New Use of an Old Agent, Reduction of Intracramal and Intraocular Pressure, The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, August, 1958, p. 22.

TRAVENOL LABORATORIES, INC.

pharmaceutical products division of BAXTER LABORATORIES, INC.



A pseudomeningocele following the ennover of a right leaves of potential



Building mass completely alsoppears within 2 hours after the intravenous of



DURING Intracranial Emergencies

UREVERT

OBSERVED TO...

Improve many prognoses

Reduce severe headache

Enlarge the operative field

Minimize brain damage

Shorten surgical intervention

Facilitate recovery

Shorten hospitalization

Brain tumors

Acute glaucoma

Cerebral edema

CNS infections

Head injuries

Hypophysectom

Trigeminal rhizotomy



Clinically developed during the past 3 years, the intracranial decompression achieved by Urevert\* permits surgical intervention and correction in many conditions where such procedures were formerly regarded as contraindicated or technically impractical. Postoperatively, its use is more expedient than ventricular puncture or drainage.

IN

NOTE: Complete information on the indications, dosage and clinical background of Urevert is available in a Product Brochure and clinical reprints. Write to Medical Department, Travenol Laboratories, Inc., Morton Grove, Illinois.

TRAVENOL LABORATORIES, INC.

pharmaceutical products division of

BAXTER LABORATORIES, INC.

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## when it's skin deep use XYLOCAINE ointment

... in nearly all external symptoms of pain, itching and burning, e.g., sunburn, minor burns, insect bites, abrasions, poison ivy and other contact dermatitis, hemorrhoids and inoperable anorectal conditions, and cracked nipples.

Xylocaine Ointment, a surface or topical anesthetic, gives fast, effective and long lasting relief. Its water-soluble, nonstaining base melts on contact with the skin, to assure immediate release of the anesthetic for fast action and it does not interfere with the healing processes.



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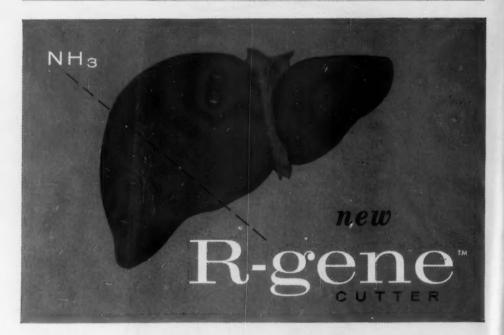
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#### helps reduce blood ammonia levels in hepatic coma

For maximum clinical effectiveness all measures to reduce ammonia intake, along with R-gene administration, should be started including reduction or withdrawal of protein intake, control of gastrointestinal bleeding, prompt removal of blood from the intestine, large oral doses of neomycin (from 4-12 Gm. daily) to reduce ammonia production in the intestine.

(The use of dextrose in conjunction with arginine apparently aids in the total ammonia utilization.)

R-gene can reduce blood ammonia levels to shorten the duration of hepatic coma or to prevent impending hepatic coma. R-gene, a solution of L-arginine, accelerates the conversion in the liver of toxic ammonium to nontoxic urea.

Improvement of the mental status of patients in hepatic coma has been reported to accompany the reduction of blood ammonia levels usually within 24 to 48 hours following arginine therapy.\*

R-gene is indicated in any disease states where elevated ammonia levels exert a toxic effect.

- in hepatic coma or impending hepatic coma
- in ammonia intoxication due to ingestion of ammonium salts
- in acute hepatic insufficiency
- following massive upper gastrointestinal hemorrhage
- in portal cirrhosis with increased intestinal nitrogenous contents
- in any hepatic encephalopathies with elevated blood ammonia levels

How Supplied: The R-gene package consists of a half liter Saftiflask® containing 400 cc. of a 5% solution of L-arginine, a 100 cc. Ambot® of 50% dextrose, and administration set.

\*Najarian, J. S., and Harper, H. A.: Am. J. Med. 21:832 (Dec.) 1956.

Detailed literature is available from your Cutter man or write to Dept. 9-19E



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betters breathing ... forestalls the crisis



DIUBLE REPORTER PROPERTIES ANY HYPERTENSION



#### RATIONALE

"It appears that there is now available in chlorothiazide a drug which is a specific antagonist to the abnormal sodium metabolism seen in the vast majority of hypertensive patients. The use of this agent [DIURIL] may stand the test of time as the most vital and specific weapon in the treatment of a relatively non-specific disease in which the only specific abnormality known is one of sodium metabolism.... Chlorothiazide now appears to be the drug of choice when initiating therapy in the average hypertensive patient."

Reinhardt, D. J.: Delaware State Med. J. 30:1, January 1958.

#### RESULTS

"We have presented a group of 48 patients previously treated with a variety of antihypertensive agents." "Upon the addition of chlorothiazide to their regimens, there was realized an additional blood pressure lowering effect of 23 mm. systolic and 11 mm. diastolic."

Bunn, W. H., Jr.: Ohio State Med. J. 54:1168, September 1958.

#### MINIMAL SIDE EFFECTS

"There is an extremely wide range between therapeutic and toxic dosage, and no significant side effects and no sensitivity to the drug as yet have been observed."
"... it seems desirable to add potassium chloride 4 Gm. per day ... in cases of hypertension..."

Herrmann, G. R., Hejtmancik, M. R., Graham, R. N. and Marburger, R. C.: Texas State J. Med. 54:639, September 1958.

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Course No. 3, CARDIAC ARRHYTHMIAS: Philadelphia General Hospital, Philadelphia, Pa.; Samuel Bellet, M.D., F.A.C.P., Director. May 22 to 24, 1959.

Course No. 4, PSYCHIATRY FOR THE INTERNIST: Psychoanalytic Institute of Baltimore and Psychiatric Institute, University of Maryland Hospital, Baltimore, Md.; Leo H. Bartemeier, M.D., F.A.C.P., and Ephraim T. Lisansky, M.D., F.A.C.P., Co-directors. June 1 to 5, 1959.

Course No. 5, SPECIAL TOPICS IN INTERNAL MEDICINE: University of Colorado Medical Center, Denver, Colo.; Gordon Meiklejohn, M.D., F.A.C.P., and C. Wesley Eisele, M.D., F.A.C.P., Co-directors. June 15 to 19, 1959.

Course No. 6, INTERNAL MEDICINE; SELECTED TOPICS: Cincinnati General Hospital, University of Cincinnati College of Medicine, Cincinnati, Ohio; Richard W. Vilter, M.D., F.A.C.P., Director, and John R. Braunstein, M.D., F.A.C.P., Associate Director. June 22 to 26, 1959.



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and

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#### With Singoserp this patient's blood pressure was controlled for the first time without side effects

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PHOTOS USED WITH PERMISSION OF THE PATIENT.

Tombstone salesman had known hypertension for 16 years; rejected by U.S. Army because of high blood pressure. Whole root rauwolfia lowered pressure satisfactorily, but patient could not tolerate side effects.

History of this patient in chart form:

History of this patient in chart form.

stuffy nose
headache
poor sleep apprehensiveness

140 130 100 80

Singoserp in a dosage of 0.5 mg. daily lowered his blood pressure to 130/80, produced no side effects. Patient feels well, works well, speaks of marked improvement in outlook and function.



# Clinical findings in 900 patients show the selective antihypertensive action of Singoserp

IN 735 PATIENTS, BLOOD PRESSURE FELL AN AVERAGE OF 30.7 mm. Hg:

- more than half of these patients suffered from moderate to severe hypertension
- more than half of the cases involved hypertension of at least 6 years' standing, with many histories of up to 20 years' duration

#### THE SIDE-EFFECTS PROBLEM WAS MINIMIZED IN MOST PATIENTS:

Chart shows gratifyingly low incidence of side effects in 233 patients given Singoserp with no other antihypertensive medication

Side Effect	Number	Per Cent
Lethargy		
Headache		2.5
Gastrointestinal upset		
Vertigo		0.8
Nasal congestion		0.4

#### DOSAGE:

In new patients: Average initial dose, 1 to 2 tablets (1 to 2 mg.) daily. Some patients may require and will tolerate 3 or more tablets daily. Maintenance dose will range from ½ to 3 tablets (0.5 to 3 mg.) daily.

In patients taking other antihypertensive medication: Add 1 to 2 Singoserp tablets (1 to 2 mg.) daily. Dosage of other agents should be revised downward to a level affording maximal control of blood pressure and minimal side effects.

SINGOSPI)°

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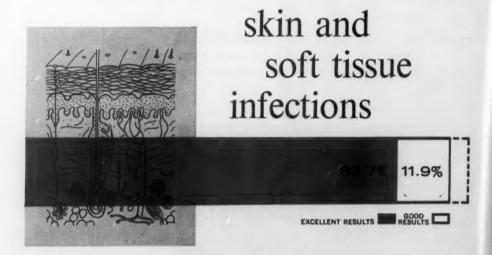
a major improvement in rauwolfia

a major advance in antihypertensive therapy In 259 cases of skin and soft tissue infections treated with triacetyloleandomycin, investigators<sup>1-8</sup> report good or excellent results in 95.6 per cent. Infections included abscesses, furuncles, carbuncles, cellulitis, infected burns, pustular acne, pyodermas, and wound infections.

Other studies, as well as wide usage, have shown that CYCLAMYCIN is also prompt and reliable therapy for respiratory and urinary tract infections due to gram-positive pathogens. CYCLAMYCIN has often proved effective against staphylococci resistant to other antibiotics.

Available in both capsule and flavored liquid form, CYCLAMYCIN is convenient to administer, readily accepted by patients of all ages.

#### a most effective antibiotic for



A "workhorse mycin" for common infections . . .

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TRIACETYLOLEANDOMYCIN, WYETH



SUPPLIED: Capsules, 125 mg. and 250 mg., vials of 36. Oral suspension, 125 mg. per 5-cc. teaspoonful, bottles of 2 fl. oz.

References: 1. Wennersten, J.R.: Antibiotic Med. 5:527 (Aug.) 1958. 2. Shubin, H., et al.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., pp. 679-684. 3. Olansky, S., and McCormick, G.E., Jr.: Antibiotics Annual 1958-1959, Medical Encyclopedia, Inc., pp. 265-267. 4. Isenberg, H., and Karelitz, S.: Ibid., pp. 284-286. 5. Mellman, W.J., et al.: Ibid., pp. 319-326. 6. Leming, B.H., Jr., et al.: Ibid., pp. 418-424. 7. Hall, W.H., and Albright, J.: In Press, Antibiot. Med. & Clin. Therap. 8. McCrumb, F.R., Jr., and Snyder, M.J.: Personal Communication.

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J. Schwab, R.S. and England, A.C.: J. Chron. Dis. 8:488-509 (Oct.) 1958.

2. Doshay, L.J. et al.: J.A.M.A. 160:348 (Feb.) 1956.

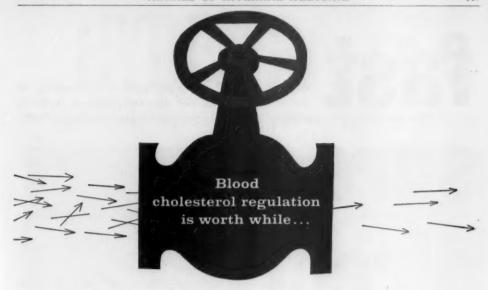
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Essential fatty acids†,...6.8 Gm. (measured as linoleic) with 2.5 I.U. of Vitamin E<sup>††</sup>

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††Added as Mixed Tocopherols Concentrate, N. F.

\*Amsterdam, B.: New York J. Med. 58:2199-2212 (July 1) 1958. Panel Discussion on Proper Nutrition for the Older Age Group, J. Am. Geriatrics Soc. 6:787-802 (Nov.) 1958. Leckert, J. T.; Donovan, C. B.; McHardy, G., and Cradic, H. E.: J. Louisiana M. Soc. 110:260-286 (Aug.) 1968.

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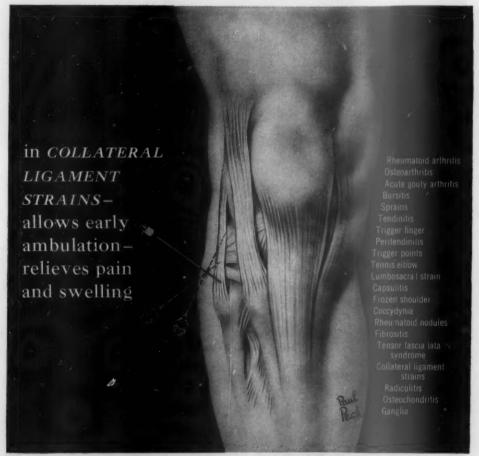
hamberlain, D. T.: Gasntercology 17:224, 1851. ock, C. W.: J.M.A., Ga. 26, 1961. a. Derome, L.: d. M.A.J. 69:532, 1963. holet, M., Goodstein, S., THE WM. S. MERRS

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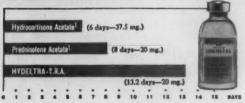
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# Is there a relationship between premature impotence and diabetes?

Yes. The incidence of premature impotence was studied in 198 diabetic men,<sup>1</sup> and found to be two to five times higher than that reported for the general population.<sup>2</sup> In many of the cases observed, impotence developed early in the history of the disease, suggesting that the possibility of diabetes mellitus be considered whenever a man complains of premature impotence.

(1) Rubin, A., and Babbott, D.: J.A.M.A. 168:498, (Oct. 4) 1958. (2) Kinsey, A. C.; Pomeroy, W. B., and Martin, C. E.: Sexual Behavior in the Human Male, Philadelphia, W. B. Saunders Company, 1948.

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Dexamyl\*—through its moodimproving and antidepressant actionhelps smooth your patient's adjustment to daily living. And, because Dexamyl' induces a sense of well-being, it often helps the depressed patient become more responsive to your counselling.

'Dexamyl', a combination of 'Dexedrine' (dextro-amphetamine sulfate, S.K.F.) and amobarbital, is available as tablets, clixir and Spansule\* sustained release capsules.

When listlessness and lethargy accompany depression, the gentle stimulation of Dexedrine\* helps revive normal interest; activity and capacity for work.

'Dexedrine' is available as tablets, elixir and 'Spansule' sustained release capsules.

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Overeating and
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- 10-14 Hour Mild Invigoration
- Predictable Weight Loss...
   a comfortable 1 to 3 lbs. a week in 9 out of 10 cases



In many instances both appetite limitation and mild invigoration ('Biphetamine') are required to effect the balance between caloric intake and energy output necessary for predictable weight reduction and control. Since 'Strasionic' release is employed, the desired therapeutic action is uniform, predictable and comfortable.

Biphetamine may be prescribed for obese patients who are hypertensive, arthritic, diabetic, pregnant, menopausal, aged; and to reduce surgical risks. Use with initial care in patients hypersensitive to sympathomimetic compounds, in cases of coronary disease or severe hypertension.

#### Single Capsule Daily Dose 10 to 14 hours before retiring



STRENGTHS

List No. 875

BIPHETAMINE®

Each black capsule contains:
d-amphetamine . . . . 10 mg.
di-amphetamine . . . . 10 mg.
as resin complexes

BIPHETAMINE®

Each black and white capsule centains d-amphetamine ..... 6.25 mg. dl-amphetamine ..... 6.25 mg. as resin complexes

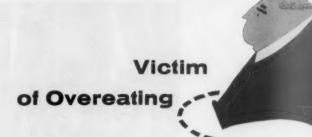
BIPHETAMINE®

Each white capsule contains: d-amphetamine .....3.75 mg. dl-amphetamine .....3.75 mg.



Rx Only. Caution: Federal law prehibits dispensing without prescription.







#### Non-Amphetamine

# STRASIONIC' ANGRETIC PHENYL-TEST - BUTYLAMINE RESIN

- 10-14 Hour Appetite Curb
- Predictable Weight Loss...
   a comfortable .221 lbs. per day in average case



in many instances, appetite limitation only ('ionamin') is required to effect the balance between caloric intake and energy output necessary for predictable weight reduction and control. Since 'Strasionic' release is employed, the desired therapeutic action is uniform, predictable and comfortable.

ionamin may be prescribed for obese patients who are arthritic, diabetic, pregnant, menopausal, aged, to reduce surgical risks, and may be used with caution in hypertensive or cardiovascular disease.

#### Single Capsule Daily Dose 10 to 14 hours before retiring



STRENGTHS

List No. 904

IONAMIN"

Each yellow capsule centains: phenyl-tert.-butylamine . . 30 mg. as a resin complex



List No. 903

IONAMIN"

Each grey and yellow capoule contains phenyl-tert,-butylamine . . 15 mg.

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Originators of 'Strasionic' (sustained ionic) Release

for all your patients starting on corticoids

Kenacort safely starts your patients off right - with all the benefits of systemic corticosteroid therapy and few side effects to worry about, Increased antiallergic, antirheumatic or anti-inflammatory activity is provided on a low dosage schedule.1-3 Clinical improvement is accomplished without water or salt retention, 1-4 or adverse effect on blood pressure.1-3.5 A low sodium diet is not necessary.4,5 Gastrointestinal disturbances are negligible<sup>2,4,5</sup> with less chance of peptic ulcer,4 and there is no psychic stimulation to distort the clinical response.1-3 This makes Kenacort particularly valuable in treating your "problem patients" - such as the obese or hypertensive and the emotionally disturbed.

- REFERENCES:
  1. Freyberg, R.H.: Berntsen, C.A., Jr., and Hollman, L.: Arth. & Rheum. 1:215 (June) 1958.
  2. Sherwood, H., and Cooke, R.A.: J. Allergy 28:97 (March), 1957.
  3. Shelley, W.B.; Harun, J.S., and Pillsbury, Dus. J.A.M.A. 187:959 (June 21) 1958.
  4. Dubois, E.L.: California Med. 89:195 (Sept.) 1956.
  8. Martung, E.F.: J.A.M.A. 187:973 (June 21) 1958.

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# Guibb Triamcinolone

# for all your patients with dermatoses requiring corticoids

Kenacort, particularly in treating inflammatory skin conditions, has also proved effective where other steroids have failed. It quickly alleviates itching, erythema, and irritation with its enhanced antiallergic, anti-inflammatory and antipruritic activity. Rapid clinical improvement is accomplished on a low dosage schedule1-3 with few side effects to worry about.1-5 (Kenacort is particularly valuable for your dermatologic patients with hypertension, cardiac disease, obesity and those prone to psychic disturbances.) **Excellent results have been reported** in treating localized neurodermatitis, contact and seborrheic dermatitis, alopecia areata, chronic eczematous eruptions - including atopy, and many cases of psoriasis.3 Because of its relative freedom from untoward reactions, Kenacort provides corticosteroid benefits to many patients who until now have been difficult to control.

#### SUPPLIED.

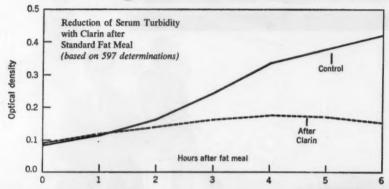
Scored tablets of 1 mg. — Bottles of 50
Scored tablets of 2 mg. — Bottles of 50

### in the management of atherosclerosis

# Clarin\* (sublication hepatheem

(sublingual heparin potassium, Leeming)

### clears lipemic serum



Each time your patients eat a substantial fat-containing meal, lipemia results. Small amounts of injected heparin will help control this increased fat content in the blood, 1.2 but widespread adoption of this method has been hampered by its inconvenience, pain, cost and the necessity for periodic checks on blood clotting time.

Now, long-term preventive heparin therapy is practical for the first time with the introduction of Clarin—which is heparin in sublingual form. Each Clarin tablet contains 1500 I.U. of heparin potassium—a sufficient amount to clear lipemic serum without affecting coagulation mechanisms.<sup>3,4</sup>

With one mint-flavored CLARIN tablet under the tongue after each meal, lipemia is regularly controlled, removing a constant source of danger to the atherosclerotic patient. He may eat safely, with less fear of dangerous results, without hard-to-follow diets.

The varied implications of CLARIN in beneficially affecting fat metabolism are obviously far-reaching. The relationship between heparin, lipid metabolism and atherosclerosis

may well be analogous to that between insulin, carbohydrate metabolism and diabetes mellitus.<sup>5</sup>

Use CLARIN to protect your atherosclerotic patients—the postcoronaries and those with early signs of coronary artery disease.

Indication: For the management of hyperlipemia associated with atherosclerosis.

**Dosage:** After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

Council on Drugs, J.A.M.A. 166:52 (Jan. 4) 1958.
 Hahn, P. F.: Science 98:19 (July 2) 1943.
 Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
 Rubio, F. A., Jr.: Personal communication.
 Engelberg, H., et al.: Circulation 13:489 (April) 1956.

\*Trade Mark. Patent applied for.

Thos. Leeming & Co., Inc.

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The patient with gastrointestinal dysfunction often finds the printed page blurred like this, because of the side effects of some antispasmodics. He may be so disturbed that he abandons treatment. But you can provide safe, effective relief of pain and spasm without risk of blurred vision with...

# Miltown + anticholinergic

direct antispasmodic action plus control of anxiety and tension without blurred vision, dry mouth or loginess associated with barbiturates, belladonna and bromides.

#### FORMULA:

each scored tablet contains: meprobamate 400 mg., tridihexethyl chloride 25 mg., (formerly supplied as the iodide).

I tablet t.i.d. with meals and 2 tablets at bedtime.



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#### IN EDEMA:

- shows greater oral effectiveness than any other class of diuretic agent
- each 25 mg. HYDRODIURIL orally is equivalent to 1.6 cc. meralluride I.M.
- has been reported to be effective even in patients who do not respond satisfactorily to other diuretics
- m has prompt onset of action with diuretic effectiveness maintained even on prolonged daily administration
- m low toxicity-extremely well tolerated
- often achieves the benefits of a low salt diet without the unpleasant restriction

Indications: Hypertension, congestive heart failure of all degrees of sever-ity, premenstrual syndrome (edema), edema and toxemia of pregnancy, renal edema—nephrosis, nephritis; cirrhosis with ascites, drug-induced edema, and as adjunctive ther-apy in the management of obesity complicated by edema.

dosage: In edema—one or two 50 mg. tablets of HYDRODIURIL once or twice a day.

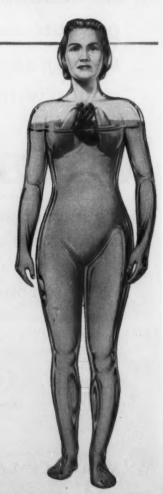
In hypertension—one or two 25 mg, tablets or one 50 mg, tablet HYDRODIURIL once or twice a day.

supplied: 25 mg, and 50 mg, scored tablets HYDRODIURIL (Hydrochlorothiazide) in bottles of 100 and 1,000.

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Additional information on HYDRODIURIL is available to the physician on request.

hibliography: 1. Esch, A. F., Wilson, I. M. and Freis, E. D.: 3,4-Dihydro-chlorothiazide: Clinical Evaluation of a New Saluretic Agent. Preliminary Report; M. Ann. District of Coulmbia 28,9 (Jan.) 1959. 2. Ford, R. V.: The Clinical Pharmacology of Hydro-chlorothiazide; Southern Med. J.52-40 (Jan.) 1959. 3. Fuchs, M. Bodi, T., Irie, S. and Moyer, J. H.: Preliminary Evaluation of Hydrochlorothiazide (Hydrochluft); M. Rec. & Ann. 51:872, (Dec.) 1958. 4. Moyer, J. H., Fuchs, M., Irie, S. and Bodi, T.: Some Observations on the Pharmacology of Hydrochlorothiazide; Am. J. Cardiol. 3:113, (Jan.) 1959.



## HYDRODIURIL (HYDROCHLOROTHIAZIDE)

- highly-active derivative of chlorothiazide
- qualitatively similar to DIURIL® but at least 10 to 12 times more potent by weight
- loss of potassium is clinically insignificant in the great majority of patients on normal diets

# HYDRO DE LE HYDROCHLOROTHIA7IDE

#### IN HYPERTENSION:

- effective by itself in some patients—markedly potentiates other antihypertensive agents
- provides background therapy to improve and simplify the management of all grades of hypertension
- has been reported by some investigators to have a greater antihypertensive effect in some patients than chlorothiazide at equivalent dosage
- does not lower blood pressure in normotensives
- reduces dosage requirements for other antihypertensive agents, often with concomitant reduction in their distressing side effects
- smooths out blood pressure fluctuations

precautions: It is important that the dosage be adjusted as frequently as the needs of the individual patient demand. When HYDRODIURIL is used with a ganglion blocking agent, it is mandatory to reduce the dose of the latter by at least 50 per cent, immediately upon adding HYDRODIURIL to the regimen.

HYDRODIURIL has shown no adverse effects on renal function; for this reason it may be used with excellent results even in patients for whom the organomercuriels are contraindicated because of renal damage.

The excretion of potassium is much lower than that of sodium or chloride and, as is the case with DIURIL®, the loss of potassium is clinically insignificant in the great majority of patients on normal diets. If indicated, potassium loss may easily be replaced by including potassium-rich foods in the diet (orange juice, bananas, etc.).



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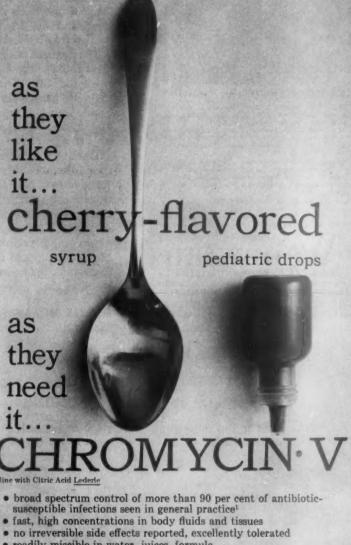
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fastest acting<sup>4</sup> controllable action 1.5 saves more lives6

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With the prompt use of Levophed, 28 per cent of patients

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· readily miscible in water, juices, formula.

ACHROMYCIN V: 10 cc. plastic dropper bottle for precise dosage; 100 mg. per cc. (20 drops). Dosage: one drop per pound body weight per day.

ACHROMYCIN V Syrup: Each teaspoonful (5 cc.) contains equiv. 125 mg. tetracycline HCl. Bottles of 2 and 16 fl. oz. Dosage: at 45 lbs., one teaspoonful 4 times daily; adjust for other weights.

1. Based on six-month National Physicians Survey.



LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY Pearl River, New York

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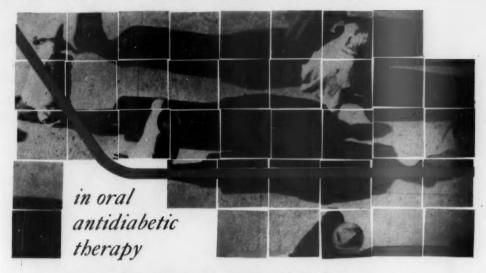
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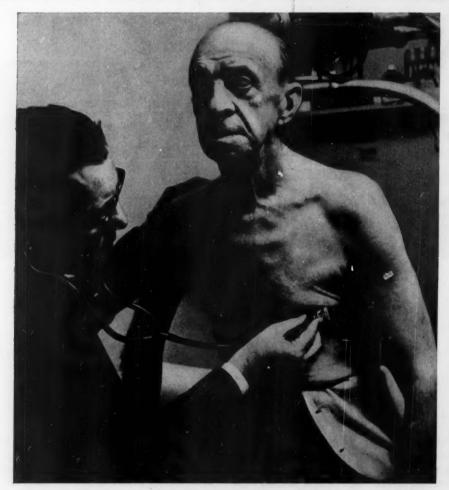
Supplied: Tablets, white, scored, 250 mg., bottles of 60 and 250; 100 mg. bottles of 100.

r, S., et al.: M. Ann. District of Columbia 27:445, 1958. 2. O'Driscoll, B. J.: J. Irish M. A. 43:323, 1958. thouse, B.: In Conference on Diabinese and Diabetes Mellitus, New York Acad. Sc., Sept. 25-27, 1958, New York, Sheppe, W. M.: West Virginia M. J. 54:467, 1958. 5. Schumacher, O. P., et al.: Cleveland Clinic Quart. 26:12,

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